

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-304**

**PHARMACOLOGY REVIEW(S)**

**Tertiary Pharmacology Review**

**By:** Paul C. Brown, Ph.D., ODE Associate Director for Pharmacology and Toxicology  
OND IO

**NDA:** 22-304

**Submission date:** January 23, 2007

**Drug:** tapentadol

**Sponsor:** Ortho-McNeil Pharmaceuticals

**Indication:** moderate to severe pain

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

**Introductory Comments:**

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

**Reproductive and developmental toxicity:**

The reviewer and supervisor agreed with the sponsor's proposed pregnancy category of C. Studies in rats and rabbits showed that tapentadol was not teratogenic in the rat but it did induce some malformations at high maternally-toxic doses in the rabbit. The reviewer and supervisor recommended that information \_\_\_\_\_

\_\_\_\_\_ be deleted from the labeling since toxicokinetic data from these studies were not available, whereas toxicokinetic data were available from subcutaneous studies and since the subcutaneous study in rabbits did show some effects at high doses. The reviewer has expressed the margin of exposures for the various studies based on a comparison of AUC in the human and animals rather than on \_\_\_\_\_ as originally proposed by the sponsor. I agree that it is preferable to use AUC comparisons.

**Carcinogenicity:**

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

**Animal Toxicology and/or Pharmacology:**

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

**Conclusions:**

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

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Paul Brown  
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PHARMACOLOGIST

11/20/08



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

### Background/Purpose

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

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

b(4)

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

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

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

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Adam Wasserman  
11/20/2008 11:33:08 AM  
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**Supervisory Pharmacologist Memorandum (#2)**

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NDA NUMBER: 22-304  
SERIAL NUMBER: 000  
DATE RECEIVED BY CENTER: 23-JAN-2008  
PRODUCT:  
    **(Proposed) Trade Name:** Not Finalized  
    **Established Name:** Tapentadol HCl  
  
INDICATION: Relief of moderate to severe acute pain  
SPONSOR: Ortho-McNeil-Janssen Pharmaceuticals, Inc;  
          Johnson & Johnson  
DOCUMENTS REVIEWED: Proposed package insert and addendum to Dr.  
                          Young's review  
REVIEW DIVISION: Division of Anesthesia, Analgesia and  
                          Rheumatology Products (HFD-170)  
PHARM/TOX REVIEWER: Kathleen A. Young, Ph.D.  
PHARM/TOX SUPERVISOR: Adam Wasserman, Ph.D.  
DIVISION DIRECTOR: Bob Rappaport, M.D.  
PROJECT MANAGER: Matthew Sullivan

## *EXECUTIVE SUMMARY*

### **I. BACKGROUND**

This memo serves to document the rationale underlying the recommendations made by the nonclinical team to the proposed package insert for Tapentadol HCl.

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       Trade Secret / Confidential (b4)

       Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

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Adam Wasserman  
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PHARMACOLOGIST



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CENTER FOR DRUG EVALUATION AND RESEARCH

**Supervisory Pharmacologist Memorandum**

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NDA NUMBER: 22-304  
SERIAL NUMBER: 000  
DATE RECEIVED BY CENTER: 1/23/2008  
PRODUCT:  
    **(Proposed) Trade Name:** N/A  
    **Established Name:** Tapentadol HCl

INDICATION: Moderate to Severe Pain  
SPONSOR: Ortho-McNeil-Janssen-Pharmaceuticals,  
Inc; Johnson & Johnson  
DOCUMENTS REVIEWED: Primary NDA review of Dr. Kathleen  
Young; electronic NDA submission  
REVIEW DIVISION: Division of Anesthesia, Analgesia and  
Rheumatology Products (HFD-170)  
PHARM/TOX REVIEWER: Kathleen A. Young, Ph.D.  
PHARM/TOX SUPERVISOR: Adam Wasserman, Ph.D.  
DIVISION DIRECTOR: Bob Rappaport, M.D.  
PROJECT MANAGER: Matthew Sullivan

## *EXECUTIVE SUMMARY*

### **I. BACKGROUND**

The present NDA has been submitted by Johnson & Johnson Pharmaceutical Research and Development on behalf of Ortho-McNeil-Janssen Pharmaceuticals, Inc. for marketing authorization of Tapentadol HCl, a centrally active  $\mu$ -opioid agonist possessing norepinephrine reuptake (NET) inhibition properties, which has been developed for the treatment of moderate to severe acute pain. Tapentadol HCl is formulated as immediate release (IR) tablets of 50, 75, and 100 mg and proposed dosing will allow for Q4h dosing (i.e. 600 mg/day with 700 mg/day allowed on the first day of use).

Tapentadol is in a similar pharmacologic class as Tramadol (Ultram®), which shares the same  $\mu$ -opioid-NET inhibition pharmacologic profile. Although Tramadol is unscheduled with the Drug Enforcement Agency, Tapentadol HCl is being proposed to be a C-II scheduled drug due to concerns of abuse potential.

b(4)

#### **A. Regulatory Summary (Pharmacology/Toxicology)**

Regulatory issues which required interaction and agreements with the Applicant during tapentadol development primarily centered on the evaluation of the major human metabolite, tapentadol-*O*-glucuronide, which due to high first pass metabolism with the oral route circulates at levels substantially higher (20-30X) than the parent at the maximum recommended human dose (MRHD). The Applicant was advised that nonclinical models would need to provide support for the safety of metabolite levels and several safety evaluations were recommended.

### **II. MAJOR NONCLINICAL ISSUES IDENTIFIED IN PRIMARY REVIEW**

#### **A. General Toxicology Findings**

##### **CNS (rat and dog)**

The primary target organ identified in all nonclinical species was the central nervous system (CNS). Observational signs were typical of a  $\mu$ -opioid agonist and/or NET inhibitor and included evidence of CNS depression (recumbency, decreased/irregular respiratory rate, and decreased activity) as well as paradoxical evidence of CNS stimulation including hyperactivity, increased sensitivity to touch/noise and enhanced escape responses, tremors and convulsions. In general, CNS observations reduced in intensity/incidence with repeated dosing indicative of tolerance – a common aspect of  $\mu$ -opioid pharmacodynamics though some effects did not show tolerance, including convulsions which may indicate a NET inhibition effect. Convulsive activity was most prominent in the dog in both short-term repeat-dose studies through the subcutaneous (SC) and oral (PO) route as well as in longer studies up to 52 weeks duration with PO dosing. Of concern, convulsions observed in the dog were associated with exposure levels that do not support human exposures. Convulsions were not seen in the rat with

PO administration; however, convulsions were observed in rat studies of CNS safety in which tapentadol was administered intravenously at high doses, and in one study demonstrated a late-developing convulsion component to the CNS safety profile. Dr. Young indicated that the levels of parent and glucuronide metabolite were below the limits of detection in both plasma and CSF at this time-point (12 hrs post-administration) and therefore the mechanism for this toxicity was unclear from the study. The Applicant's hypothesis that this could be caused by an unidentified metabolite in "deeper CNS compartments" was not investigated. A direct pro-convulsant effect for the parent or primary glucuronide metabolite was also confirmed with demonstration that tapentadol lowered seizure-threshold (as measured by increased incidence) when administered intravenously prior to injection of the convulsant pentylenetetrazole. Although one study in rat indicated these convulsions were not prevented by pre-treatment with the broad-spectrum opioid receptor antagonist naloxone administered intraperitoneally (IP) (but were inhibited by diazepam and phenobarbital), a second study reported that these observations (and other clinical signs) were blocked dose-dependently by IP or IV naloxone. This distinction is important in that attribution of convulsions to a  $\mu$ -opioid effect places the risk within the known profile of opioids and not a direct effect of secondary pharmacology of the molecule for which the human relevance is less clear by prior clinical experience. Upon examination of the two studies, it appears that the inconsistency may be due to the different routes of administration and resulting naloxone exposures; this is supported by re-testing of the dose/IP route used in the initial exploratory study which was previously only moderately effective. In contrast, IV naloxone clearly inhibited the convulsive effect (as well as with most of the other clinical signs) associated with high dose IV tapentadol in the rat, supporting the Applicant's contention that this is predominantly a  $\mu$ -opioid-mediated effect. Dr. Young's review notes that convulsions observed in the 52-week chronic toxicity study in dog were reversible with naloxone administration, strengthening a opioid-mechanism argument. That evidence of tolerance did not occur in both species is of some concern and may indicate that some aspect of this toxicity is mediated by NET inhibition. Nevertheless, a similar drug – tramadol – which also has a NET inhibitory component in addition to the  $\mu$ -opioid activity has a known clinical adverse event (AE) profile which includes seizures, especially with overdose. Although it might have been best to have a head-to-head comparison of the pro-convulsant activities of tapentadol relative to tramadol, I agree with Dr. Young that the clinical safety database of ~3500 patients without demonstration of seizure activity is somewhat reassuring. Nevertheless, seizures were not reported in clinical studies of tramadol and tramadol ER (500+ and 3000+ exposures) clinical trials but seizures were detected through post-marketing reports and as the propensity of this class (both  $\mu$ -opioid as well as the  $\mu$ -opioid/NET inhibition) are well known and can be addressed in the product label as it is clearly communicated in the Ultram® (tramadol) label. Intriguingly, it is noted that the label for tramadol states that convulsions in animals was ameliorated by barbiturates and benzodiazepines but, in contrast to tapentadol, was worsened by administration of naloxone. This latter finding may be expected if convulsions were primarily or exclusively driven by NET inhibition and opioid-induced

CNS depression is blocked with an antagonist. It is possible the pharmacologic foundation of the convulsions observed with tapentadol is slightly different, however.

#### **Liver (rodent)**

Liver findings described in Dr. Young's review of the rodent (mouse and rat) toxicology data appears to most likely be explained by hepatic enzyme induction, likely of Phase 2 rather than Phase 1 metabolizing enzymes. Evidence of increased liver weight and centrilobular hepatocellular hypertrophy was noted in the mouse 13-week study and rat 13- and 26-week studies with correlative increased LFTs. Hepatic necrosis was not generally observed in rodent toxicology studies with the exception of a 4-week high-dose IV study in the rat and with very high PO doses in the mouse ( $\geq 500$  mg/kg/day). Fatty deposits in the liver was noted at all dose levels - including controls - in the chronic rat study though the elevated incidence in the high dose group may reflect increased lipid transport from periphery to liver to satisfy energy requirements as this was coincident with significant reduction of body weight and early reduction in food consumption. It is worth noting that hepatic necrosis was not observed in the treatment group receiving the highest dose (450 mg/kg/day) which demonstrated large increases in LFTs and this group was terminated early at study week (SW)13 due to mortality in the face of severe CNS signs. The 300 mg/kg/day level which provide a significant margin of exposure over human clinical dose, while not well tolerated due to CNS effects, also showed no evidence of necrotic changes or significant hepatic pathology at the end of 26 weeks of dosing. All hepatic changes were considered reversible upon examination after 8-week treatment-free recovery period. Hepatic effects were not an observed toxicity in the dog studies through the SC or PO route, including the pivotal 52-week chronic oral study. It must be noted that due to poor CNS tolerability that the maximum tolerated dose provides limited assurance of safety as this dose was associated with an AUC that is slightly below or at best roughly equivalent to the human AUC; therefore, no safety margins could be developed to support safety.

#### **Cardiovascular system (dog)**

Nonclinical safety studies provided an equivocal signal for cardiovascular toxicity. In vitro evaluation of hERG channel blockade identified a potential for blockade as well as prolongation of the action potential in isolated cardiac tissue though this was reached at high concentrations ( $\geq 8$   $\mu\text{g/mL}$ ;  $\geq 70$ -fold above human  $C_{\text{max}}$  at MRHD). No prolongation was noted in other isolated or more intact in vitro/ex vivo preparations such as in guinea pig papillary muscles or isolated, spontaneously beating rabbit hearts. The Applicant also examined the glucuronide metabolite - critical as the circulating levels are far in excess of the parent - and determined that this species does not block the hERG channel or prolong action potential duration (APD) in vitro. In vivo the cardiovascular profile was mixed but appeared to depend on the state of consciousness: Hypotension and decreased cardiac output was observed in anesthetized preparations while in conscious animals (rat and dog) increased HR and BP was observed. In a 13-week and in the 52-week chronic dog study there was mild QT prolongation noted at the highest dose evaluated (+7-10% by Van de Water's or Fridericia's correction associated with a  $C_{\text{max}}$  1-

2X human levels; glucuronide  $C_{max}$  16X human levels). No significant effect on ECG was apparent at the mid-doses though  $C_{max}$  at this level does not provide support for human use (.25 - .40X human maximal concentrations). Nevertheless, this concern has been largely addressed in clinical trials, and a thorough QT study at supra-therapeutic levels was negative according to the clinical review of Dr. Ellen Fields.

#### **Gastrointestinal system (rat and dog)**

GI toxicity noted by Dr. Young primarily involved typical alterations in food consumption and slowed transit associated with  $\mu$ -opioid agonist drugs but also was suggested by local toxicity in which dogs administered tapentadol by the oral route at high dose displayed activated lymphocytes in Peyer's patches of the intestines and gastric mucosa. The significance of these findings is not clear: they did not appear in all oral studies and the findings reversed in studies in which a recovery group was included. A general local intolerance was observed with parenteral dosing, particularly SC. However, administration of tapentadol did appear to generate GI hemorrhage in a 13-week study and this would not be expected to be a result of local intolerability.

#### **Adrenal gland**

Adrenocortical hypertrophy was observed in a 13-week dog study by the PO route. Findings were only observed in males, were noted at lower incidence and severity in controls, but was not associated with any overall changes in adrenal weight and histological abnormalities were absent in recovery group animals. Thymic atrophy was also noted and the Applicant proposed a stress response as the principal underlying explanation for both findings. Neither effect was observed in the 52-week chronic dog study which suggests these findings have limited relevance.

#### ***B. Genetic Toxicology Findings***

The Applicant conducted the standard battery of genotoxicity tests and due to a positive finding in an initial chromosomal aberration assay, this assay was repeated, found to be negative, and argued that the negative follow-up study in combination with a negative in vivo micronucleus assay in rat as well as a negative Unscheduled DNA Synthesis (UDS) assay argued that the weight-of-evidence suggests tapentadol is not genotoxic. Dr. Young notes that the positive finding in the chromosomal aberration assay occurred only in the condition in which the target cells (V79 hamster fibroblasts) were exposed to tapentadol in the presence of a rat liver (S9) metabolizing system. She suggests that this indicates a genotoxic potential by an unidentified metabolite under the conditions of the assay and further that the potential for clastogenicity by tapentadol in humans cannot be ruled out. While it is perhaps likely that the clastogenic finding is associated with a metabolite (as conditions without the S9 system were negative), it is noted that this initial study did not use current methodologies – in particular the incubation duration with S9 was far in excess of that used in current protocols (18 and 28 hr vs. 3-6 hr, respectively) and long exposure to this preparation has been associated with false positive results (Kirkland et al., 1989). When current study protocols were used there was no evidence of

clastogenicity. While this is reassuring, it is also important to note that the rat liver S9 preparation may produce metabolites "quite different from those produced by normal human liver metabolism" (Kirkland et al., 2007) and furthermore the relative levels of CYP1A and CYP2B compared to other CYP isoforms are greater than in standard liver tissue which may lead to the non-representative profile of metabolite exposure. Most important for the evaluation of tapentadol, however, is that in the rat liver S9 preparation there is practically no activity of Phase 2 hepatic enzymes. Therefore, it would be expected that in this condition there is virtually no exposure to the primary metabolite tapentadol-O-glucuronide (and therefore any positive finding is unlikely to be due to this metabolite, even if not an artifact of an outdated protocol). This does of course raise the point that the in vitro evaluations of genotoxicity (Ames assay, chromosomal aberration assay) did not evaluate the glucuronide metabolite; however, this would have been evaluated in the in vivo micronucleus assay and UDS assay, both of which were negative. Therefore, I agree with the Applicant that the findings suggest tapentadol is not genotoxic under current accepted assay conditions. I agree with Dr. Young that the negative carcinogenicity data adds further reassurance.

### *C. Carcinogenicity Findings*

Tapentadol administration was not associated with tumor development in 2-year rat and mouse bioassays in the evaluation by Dr. Young; an assessment to which the Executive Carcinogenicity Assessment Committee concurred.

### *D. Reproductive Toxicology Findings*

#### *Fertility and Early Embryonic Development (Segment 1)*

No statistically significant effects were noted on fertility or reproductive performance following IV administration of tapentadol (0, 3, 6, or 12 mg/kg) prior to mating in both male and female rats through the early part of gestation in females according to Dr. Young's review. These study endpoints (fertility, reproductive performance) are not especially sensitive measures in highly multiparous species like rodents, however. As noted by Dr. Young, statistically significant and dose-related pre-implantation loss was observed in the study at  $\geq$  MD level as was significantly increased post-implantation loss (deaths) during the embryonic or fetal stage which resulted in a statistically significant decrease in the number of living fetuses in the HD group. Dr. Young concurred with the Applicant that embryofetal toxicity was likely explained by the significant maternal toxicity present in pregnant dams in the MD and HD treatment groups. There was significantly reduced body weight gain and decreased food consumption in these treated groups compared with controls and this may be a partial explanation. However, the effects do not appear to be dramatic (+1 vs. 2.9% body weight gain in treated vs. control animals; -3 to -9% food consumption vs. controls; with most observed of the decline prior to mating); opioids have known effects on fertility through actions on the hypothalamic-pituitary-gonadal axis and it would seem possible or perhaps likely that this route may also be involved. No evaluation of pituitary hormones or sex steroids was provided to examine this possibility directly, however. Regarding effects on male reproductive capacity, treatment-related pathology was not noted in male reproductive

organs though the most sensitive measure of effects involving the male reproductive system require evaluating the complete stages of the spermatogenic cycle which was not undertaken. As effects observed do not suggest a strong male-associated component this is not necessary for study validity. Toxicokinetic evaluation was not performed for the study or in a dose-range finding study, therefore a comparison to human exposure at the MRHD is not straightforward. Dr. Young notes a 4-week IV study with similar dosing (0, 3, 7, or 15 mg/kg) which she indicates would only provide a safety margin of ~0.4X MRHD by AUC comparison. The label will indicate this lack of a safety/exposure margin.

Overall, the results of these studies suggest that tapentadol does not present a significant risk for fertility at the admittedly low exposure levels achieved though embryofetal toxicity should be described in the label as part of this discussion. It should be noted that these findings are generally in line with other opioids and appear to be very similar to findings described in the package insert for the pharmacologically- and structurally-related tramadol.

#### *Embryofetal development (Segment 2)*

Studies to evaluate embryofetal development were conducted by both the SC and IV route in rats and rabbits. Tapentadol was not associated with embryofetal malformations in the rat with either route when administered at dose levels (up to 15 mg/kg/day IV or 20 mg BID SC) which produce significant maternal toxicity including lethality. These studies indicate the absence of teratogenicity in the rat with maternal dose levels producing 3-fold the AUC exposure observed at the MRHD. Evidence of embryofetal toxicity included delays in skeletal maturation (i.e. reduced ossification). I concur with both Dr. Young's review and the Applicant that these probably reflect a secondary outcome of maternally toxic doses. Evaluation of tapentadol in the rabbit, however, revealed teratogenicity though this occurred only in the setting of very significant maternal toxicity. An IV study conducted with doses up to 9 mg/kg/day IV (once daily) did not detect malformations even at the high dose which was associated with moderate to severe CNS signs such as tremors and opisthotonus. The examination conducted did not appear to evaluate visceral tissues (only skeletal and external structures were evaluated). A follow-up study with dosing up to 12 mg/kg/BID (i.e. 24 mg/kg/day) by the SC route produced runts at the MD and HD and identified multiple internal visceral malformations in runts and non-runt fetuses. In addition to evidence of skeletal delays and other variations, malformations such as gastroschisis/thoracogastroschisis, amelia/phocomelia, and cleft palate was observed at  $\geq 10$  mg/kg/day; albepharis, encephalopathy, and spina bifida in the 24 mg/kg/day fetuses. Overall, fetal viability was also compromised. Findings were observed at dose levels which were associated with significant maternal toxicity as indicated by transiently decreased food consumption (-49, -77, and -92% vs. controls over dosing period of Gestation days 6-20), body weight loss (-11 to -18%), and abdominal position after dosing. The Applicant appears to make two arguments at the same time: 1) Malformations are likely due to severe maternal toxicity; and/or 2) Malformations are within the historical control data for the laboratory and species. Dr. Young indicates that either may be true, and the Applicant has provided

literature and historical control data to support both arguments. Despite the findings being largely within the HCD of the laboratory/species, I do not agree that the findings are likely to represent incidental background findings. Data clearly indicates that a dose-effect is observed for malformations (incidence of 0, 0, 2, and 6 fetuses from control, LD, MD and HD litters). I do agree that the findings are likely caused by nutritional deficits observed in dams at these doses and that tapentadol does not appear to be a direct reproductive teratogen. These findings will be described in the package insert along with the information on maternal toxicity. Toxicokinetic evaluation indicates that the NOAEL dose is associated with an exposure that is roughly equivalent to that observed in the human at the MRHD. The package insert for Ultram® does not describe malformations though it is unclear if the doses explored produced a similar degree of maternal toxicity.

*Pre- and Postnatal Developmental Development (Segment 3)*

Oral administration of tapentadol up to 150 mg BID to pregnant rats through parturition and lactation resulted in significant maternal toxicity with doses of  $\geq 75$  mg BID. Pup body weight was significantly reduced in the (maternal) high dose treatment group and increased pup mortality over the first 4 days post-birth was noted at  $\geq 25$  mg BID. No significant postnatal developmental effects on neurobehavioral or reproductive parameters were noted in surviving progeny. These findings are described in the Applicant's proposed label

\_\_\_\_\_ and provide a false safety margin which is actually absent when using toxicokinetic comparison. Dr. Young has appropriately noted this issue. Again, it is useful to note that the package insert for Ultram® describes similar results though safety margins are based on BSA.

*Other Issues*

The Applicant conducted a pharmacologic screen of major and minor metabolites and found that the major metabolite tapentadol-*O*-glucuronide did not bind to opioid receptors or any other screened receptor or enzyme. Supporting this apparent lack of pharmacology, tapentadol-*O*-glucuronide was without effect in a nonclinical pain model for which opioids, including the tapentadol parent, is active. Further evaluation of the major metabolite in cardiovascular safety pharmacology studies demonstrated an absence of effect *in vitro* on hERG channel as well as in an Action Potential Duration evaluation in isolated cardiac tissue. The applicant furthermore provided toxicokinetic data that established that nonclinical models used in toxicology studies efficiently produced the metabolite tapentadol-*O*-glucuronide at levels which exceed the human exposure.

Tapentadol is a  $\mu$ -opioid agonist and therefore is considered to have significant abuse liability. The proposed scheduling of tapentadol as a C-II substance is perhaps merited (see review by Controlled Substance Staff) though it is worth noting that the very similar  $\mu$ -opioid agonist/NET inhibitor tramadol is currently unscheduled.

### III. ADVISORY COMMITTEE ISSUES

N/A

### IV. RECOMMENDATIONS

#### A. Recommendation on approvability

I concur with the recommendation made by Dr. Kathleen Young that the application may be approved from the nonclinical perspective.

#### B. Recommendation for nonclinical studies

I am in agreement with Dr. Young that no further nonclinical studies are necessary for approval or as post-marketing commitments/requirements.

#### C. Recommendations on labeling

I concur with the general recommendations made by Dr. Young. As the metabolite tapentadol- $\alpha$ -glucuronide is not an active metabolite, however, I do not believe we need to express safety/exposure margins in the label for this species. A separate addendum to this supervisory memo will be submitted to address specific labeling language.

### *REFERENCES*

Kirland DJ, Marshall RR, McEnaney S, Bidgood J, Rutter A, Mullineux S. Aroclor-1254-induced rat-liver S9 causes chromosomal aberrations in CHO cells but not human lymphocytes: a role for active oxygen? *Mutation Research* 214(1):115-22, 1989.

Kirkland D, Pfuhrer S, Tweats D, Aardema M, Corvi R, Darroudi F, Elhajouji A, Glatt H, Hastwell P, Hayashi M, Kasper P, Kirchner S, Lynch A, Marzin D, Maurici D, Meunier JR, Muller L, Nohynek G, Parry J, Parry E, Thybaud V, Tice R, Benthem J, Vanparys P, White P. How to reduce false positive results when undertaking *in vitro* genotoxicity testing and thus avoid unnecessary follow-up animal tests: Report of an ECVAM Workshop. *Mutation Research* 628(1):31-55, 2007.

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Adam Wasserman  
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PHARMACOLOGIST

The application may be approved from the Nonclinical perspective.

## PHARMACOLOGY/TOXICOLOGY REVIEW

**NDA number:** 22-304

**Review number:** 2

**Sequence number** 000 / January 23, 2008 / Original New Drug Application

**Information to sponsor:** Yes ( ) No (x)

**Sponsor and/or agent:** Ortho-McNeil Pharmaceutical, Inc.

**Manufacturer for drug substance:** Janssen Ortho, LLC, State Road 933, KM 0.1, Gurabo, PR 00778

**Reviewer name:** Kathleen Young, Ph.D.

**Division name:** Division of Anesthesia, Analgesia, and Rheumatology Products

**HFD #:** 170

**Review completion date:** October 13, 2008

### Drug:

Trade name: NA

Generic name: Tapentadol HCl

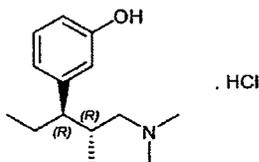
Code names: BN-200, BN 200, BN200, CG5503, R331333, JNJ-26120211-AAC

Chemical name: 3-[(1R,2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol

CAS registry number: 175591-09-0

Molecular formula/molecular weight: C<sub>14</sub>H<sub>23</sub>NO·HCl / 257.80

Structure:



**Relevant INDs/NDAs/DMFs:** IND 61,345

**Drug class:** Mu-Opioid receptor (MOR) agonist/norepinephrine (NE) re-uptake inhibitor

**Indication:** Treatment of moderate to severe acute pain

**Route of administration:** Oral

**Proposed use:** For the treatment of moderate to severe pain at 50, 75, or 100 mg every 4-6 hours, with one additional dose within 1 hour of the first dose on the first day of treatment, if needed. Total daily dose of up to 700 mg on Day 1, and 600 mg on subsequent days.

**Disclaimer:** The tabular and graphical information are taken from the original NDA submission, unless cited otherwise.

**Recommendations on labeling conveyed in the Original NDA Review of  
September 24, 3008**

*Revisions to the sections on Pregnancy, Carcinogenesis, Mutagenesis, Impairment of Fertility, and Animal Toxicology and/or Pharmacology are needed, but no substantive changes are being made to that proposed. More specific characterization of the embryofetal developmental toxicity study in rabbit will be included in the Section 8.1 Pregnancy. Potential relationship of the systemic effects of tapentadol observed in the nonclinical toxicology studies to NE reuptake inhibition will be included in Section 13.2 Animal Toxicology and/or Pharmacology. Exposure margins will be presented using an AUC basis instead of  $C_{max}$  basis, where appropriate. Inclusion of safety margins for the tapentadol O-glucuronide metabolite will be recommended. Detailed recommendations for revisions to the label will be described in a separate Labeling Review.*

Subsequent to the original NDA review recommendations, above, it was determined not to be necessary to include the exposure margins for the metabolite tapentadol O-glucuronide in the label; this metabolite was found not to bind opioid receptors or other screened receptors or enzymes, is not pharmacodynamically active; there were no effects by the glucuronide metabolite in nonclinical pain models and cardiovascular safety pharmacology studies on hERG channel *in vitro* and in isolated cardiac tissue. The following revisions to the proposed Product Label are provided below:

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ON ORIGINAL**

4 Page(s) Withheld

       Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

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this page is the manifestation of the electronic signature.**  
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/s/

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Kathleen Young  
10/23/2008 12:08:37 PM  
PHARMACOLOGIST

Adam Wasserman  
10/23/2008 12:44:20 PM  
PHARMACOLOGIST



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

**PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION**

NDA NUMBER: 22-304  
SERIAL NUMBER: 000  
DATE RECEIVED BY CENTER: 01/23/08  
PRODUCT: Tapentadol HCl  
INTENDED CLINICAL POPULATION: Patients with moderate to severe pain  
SPONSOR: Ortho-McNeil Pharmaceutical, Inc.  
DOCUMENTS REVIEWED: Electronic Submission  
REVIEW DIVISION: Division of Anesthesia, Analgesia, and  
Rheumatology Drug Products (HFD-170)  
PHARM/TOX REVIEWER: Kathleen Young, Ph.D.  
PHARM/TOX SUPERVISOR: Adam Wasserman, Ph.D.  
DIVISION DIRECTOR: Bob Rappaport, M.D.  
PROJECT MANAGER: Matthew Sullivan

Date of review submission to Division File System (DFS): September 22, 2008

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## **EXECUTIVE SUMMARY**

### **1. Background**

Tapentadol HCl, a new molecular entity is a centrally acting analgesic for the treatment of moderate to severe, acute pain at oral doses of 100 mg up to 6 times daily (600 mg/day), and up 7 times on the first day of treatment (700 mg). Tapentadol is a pure enantiomer without observable enantiomeric interconversion and with no clinically relevant active metabolites, and is freely soluble in water, hydrochloric acid 0.1N, and intestinal fluid. The rationale for development of this drug product is a potential for enhanced mu-opioid induced analgesic activity by interaction with norepinephrine transmission with fewer adverse effects that are usually associated with treatment using more selective mu-agonist agents, such as morphine and fentanyl.

### **2. Recommendations**

#### **2.1 Recommendation on approvability**

Tapentadol HCl can be approved for the proposed indication under NDA 22-304 from a pharmacology and toxicology perspective.

#### **2.2 Recommendation for nonclinical studies**

The appropriate nonclinical studies were conducted in support of the safety and labeling of Immediate Release Tapentadol HCl for the clinical indication as proposed under NDA 22-304. No further nonclinical studies are needed for marketing approval, at this time.

#### **2.3 Recommendations on labeling**

Revisions to the sections on Pregnancy, Carcinogenesis, Mutagenesis, Impairment of Fertility, and Animal Toxicology and/or Pharmacology are needed, but no substantive changes are being made to that proposed. More specific characterization of the embryofetal developmental toxicity study in rabbit will be included in the Section 8.1 Pregnancy. Potential relationship of the systemic effects of tapentadol observed in the nonclinical toxicology studies to NE reuptake inhibition will be included in Section 13.2 Animal Toxicology and/or Pharmacology. Exposure margins will be presented using an AUC basis instead of ~~—~~ basis, where appropriate. Inclusion of safety margins for the tapentadol O-glucuronide metabolite will be recommended. Detailed recommendations for revisions to the label will be described in a separate Labeling Review.

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### 3. Summary of nonclinical findings

#### 3.1 Brief overview of nonclinical findings

The results of *in vitro* receptor-, ion channel-, and neurotransmitter transporter-binding studies on tapentadol showed highest affinity for the mu-opioid and sigma (S2) receptors and norepinephrine transporter, with minimal binding to all other sites tested. Mu-opioid agonist activity was demonstrated *ex vivo* by inhibition of the twitch reaction in isolated guinea pig ileum, that was reversed by the opioid antagonist naloxone.

Tapentadol analgesic activity was investigated *in vivo*, using models of acute antinociception and inflammatory and neuropathic pain models in mice, rats, and rabbits. The results of these studies demonstrated efficacy in the tail-flick, phenylquinone writhing, hot-plate and tooth pulp stimulation tests with approximately 1/4X-1/2X the potency of morphine and 3X-5x that by tramadol. By the oral (PO) route, tapentadol was approximately equipotent to morphine analgesic effects in these assays. The oral activity of tapentadol was 2%-8%, with a maximum effect at approximately 20 minutes and duration of action of 60-90 minutes. In *in vivo* models of inflammatory and neuropathic pain using the paw-pressure test, formalin test and chronic constriction injury models in rats, tapentadol showed approximately 1/2 the potency of morphine and 1/4X-1X that of tramadol by the intraperitoneal (IP) and intravenous (IV) routes. Support for a mu-opioid receptor mechanism of action was shown by naloxone blockade, but not alpha2-receptor antagonist (yohimbine) and the serotonin-2A-C antagonist (ritanserin) blockade of the acute antinociceptive effects.

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.

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 ( $ED_{50} > 100$  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  $\geq 12$  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 ( $IC_{50} = 36.14$   $\mu$ M) 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  $\mu$ M in isolated New Zealand White rabbit papillary muscle, and was shortened at 10-100  $\mu$ M, 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 atrio-ventricular 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  $CO_2$ -induced respiratory stimulation, with corresponding increases in arterial blood  $CO_2$  partial pressure and decreased  $pO_2$  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.

The target organs of toxicity in the toxicology studies in rat were the central nervous system (CNS) and liver. The  $LD_{50}$  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.

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

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. Thorough description of the findings is needed in the product label.

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.

### 3.2 Pharmacologic activity

Tapentadol is an agonist at the mu-opioid and sigma2 receptors, and inhibits noradrenaline 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 antinociception 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 tooth pulp 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.

Secondary pharmacodynamic studies demonstrated drug class effects characteristic of those my 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.

### 3.3 Nonclinical safety issues relevant to clinical use

The target organs of tapentadol toxicity were identified in the central nervous system (CNS), hepatic, cardiovascular, and gastrointestinal (GI) effects in the nonclinical studies. Additionally, there were slight signals for potential clastogenicity by a tapentadol metabolite in the evaluation of genetic toxicology, and for adverse effects on pregnancy and embryo-fetal development in rabbits.

The results of the Safety Pharmacology and Toxicology evaluations showed dose-related CNS depression across species, doses, routes and durations of treatment. The clinical signs noted, including sedation and labored breathing, suggest potential CNS sedation in clinical treatment. Treatment-related convulsions were observed in rats given high dose IV tapentadol, and in dogs dosed by SC and oral routes at doses providing low safety margins for the proposed maximum recommended human dose. It should be noted that convulsions, cyanosis and deaths were observed after complete clearance of parent drug and the glucuronide metabolite from plasma and CSF (at >12 hours after injection) in a concentration-effect CNS safety pharmacology study in rat given high dose IV injections (15 mg/kg). This finding was not further explored in the nonclinical study program, but the Sponsor provided speculation that the findings may have been related to potential products of parent drug or metabolite enrichment in deeper CNS compartments, not detected in plasma and CSF. \_\_\_\_\_ but is not considered to be an approvability issue at this time, because there was no evidence of delayed emergence of convulsions and deaths in the absence of detectable plasma drug and metabolite levels in the other safety pharmacology and toxicology studies in rat and dog, complete clearance of radioactivity from CNS within 8 hours was demonstrated in whole body autoradiography assessment, there was no evidence of histopathologic neurotoxicity in the microscopic examinations in brain in the toxicology studies, and there were no reports of seizures in the clinical studies. Patients should be adequately informed to use caution, particularly when driving and operating dangerous machinery. There may be increased risk of serious adverse CNS effects of respiratory depression and seizures, and for cardiac arrhythmias, in susceptible patients and in the event of overdose.

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QT prolongation has been associated with norepinephrine reuptake inhibition by other drugs, and is associated with drug potency at the rapidly-activating delayed-rectifier potassium current at the  $I_{Kr}$  receptor. Tapentadol was shown to inhibit norepinephrine reuptake in the pharmacology studies, and is one of the proposed pharmacodynamic mechanisms action for analgesia in this submission. The results of several nonclinical studies suggest a potential for treatment-induced cardiac findings including QT interval prolongation and arrhythmias as multiple tapentadol signals were found *in vitro* and *in vivo* in the toxicology studies in dog. The results of a study in Chinese Hamster Ovary cells transfected with the hERG channel showed reduced the rapid component of the delayed rectifying potassium current ( $IC_{50} = 7978$  mcg/L, approximately 68 times the

Cmax at steady state at the MRHD of 600 mg/day). *Ex vivo* studies in isolated cardiac tissues showed prolongation of the action potential duration in isolated rabbit papillary muscles, bradycardia with slowing of atrio-ventricular conduction and ventricular depolarization in the spontaneously beating guinea pig Langendorff preparation, negative chronotropic and inotropic effects in isolated atrial and papillary muscle preparations, and reduced isometric aortic contractions in potassium-depolarized rat aortic strips with lidocaine-blocked sodium channels. The Safety Pharmacology studies conducted in the conscious and anesthetized dog revealed no prolongation effects on QT and corrected (QTc) interval after oral administration of tapentadol, but QT prolongation was observed in several toxicology studies in the conscious dog, including when tapentadol was given by subcutaneous injection in the 3-month study (NOEL = 4 mg/kg/day), and orally for up to 52 weeks (NOEL 30 mg/kg/day). There was some tolerance development to the effects on QT interval, in a 3-month study. The potential for QT prolongation was addressed clinically during drug development, and found to be negative in the definitive clinical thorough QT prolongation studies (Studies HP5503/25 and R1331333-PAI-1018). However, the no effect levels (NOEL) for QT prolongation in the subcutaneous and oral toxicology studies in dog provide no safety margin for human exposure, approximately 0.04 to 0.2, based on comparative systemic exposure at the MRHD, suggestive of human risk.

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Treatment-related hepatotoxicity was observed to a greater extent in the rats than in the dogs. This might be predicted, if these effects can be attributed to adaptations from increased hepatic metabolic activity as proposed and demonstrated by more extensive hepatic metabolism of tapentadol in the rats than in the dogs. Tapentadol is metabolized to a lesser extent in humans than in any of the animal species tested, and therefore may be less likely to show treatment-related hepatotoxicity related to increased liver metabolic activity. GI findings in the Safety Pharmacology studies in rodent and in the toxicology studies in dog suggest the potential for tapentadol-induced constipation and GI irritation with prolonged or excessive use.

Tapentadol showed no evidence of genotoxic potential in the Ames test and *in vivo* in the Mouse Micronucleus test. However, the results were equivocal in the Chromosome Aberration assay in Chinese Hamster Ovary (CHO) V79 cells. Tapentadol was clastogenic in the first of two independent assays at concentrations greater than 1000 mcg/ml in the presence of metabolic activation with S9. These results suggest genotoxic potential by an unidentified metabolite under the conditions of the study. A second assay in CHO cells, conducted to further explore the results of the positive findings in the Chromosome Aberration assay, revealed no increases in the frequencies of cells with aberrations at concentrations of up to the maximum tested of 1500 mcg/ml for 4 hours without S9 and up to 1000 mcg/ml for 4 hours and 300 mcg/ml for 18 hours exposure with S9 mix. However, the potential for clastogenicity by tapentadol in humans cannot be ruled out. Minor revisions will be needed for the description of treatment-related

genetic toxicity study findings in the proposed label. Tapentadol was negative for carcinogenicity in 2-year studies in mice and rats.

The results of the Embryo-Fetal Development study in Himalayan rabbits administered tapentadol by subcutaneous injection during organogenesis showed dose-related increases in the incidence of runts and multiple malformations that included thoracogastroschisis, prolapsed organs, amelia, phocomelia, encephalocele, spina bifida, cleft palate, ablepharia, and skeletal malformations. Although the malformations were observed predominantly in fetuses of dams that showed severe treatment-induced maternal toxicity, not all dams showing severe toxicity had fetuses with malformations. The incidences of malformations were within the upper limits of historical control range for the laboratory provided by the Sponsor, except for ablepharia which slightly exceeded the upper historical range. The findings in the subcutaneous embryo-fetal development study in rat were negative for malformation. However, a potential for tapentadol-induced teratogenicity cannot be entirely ruled out. Minor revisions to the description of these findings in the proposed label will be needed. It is noted, that no external and skeletal malformations were observed in rabbits given tapentadol by intravenous injections at up to maximum tolerated doses during organogenesis, in another study.

The CNS and GI target organ toxicities observed in the studies on tapentadol were characteristic of those observed by mu-opioid agonist drugs as a class. QT prolongation effects in the toxicity studies in dog may be associated with tapentadol effects on NE reuptake inhibition as well, as these have been observed by other drugs that inhibit NE reuptake. The adverse effects in liver are attributed, at least in part to adaptations related to increased hepatic metabolic enzyme activity that was also shown to be more extensive in the animal species tested than in humans.

The target organ findings were at doses providing low or absent safety margins to support the proposed maximum recommended human dose (MRHD). However, it should be noted that several of the target organ findings, such as treatment-related convulsions and QT prolongation were addressed in human studies during clinical development of the proposed drug product. Potential adverse hepatic effects could be monitored to some extent during clinical administration, by periodic clinical laboratory assessments. The target organ effects in the nonclinical studies were reversible during the recovery periods at the end of the treatment periods, and some tolerance developed to tapentadol-induced CNS clinical signs, except for convulsions. The feasibility of monitoring for potential treatment-induced convulsions, clastogenicity and potential adverse effects on pregnancy and embryo-fetal development may be low in an outpatient population however, and therefore should be clearly described in the appropriate precautionary sections of the product label.

### ***III. Administrative***

A. Reviewer signature: \_\_\_\_\_

Reviewer: Kathleen Young, Ph.D.

NDA No. 22-304

B. Supervisor signature: Concurrence - \_\_\_\_\_

\_\_\_\_\_

Non-Concurrence - \_\_\_\_\_

(see memo attached)

C. cc: list:

**APPEARS THIS WAY  
ON ORIGINAL**

## PHARMACOLOGY/TOXICOLOGY REVIEW

### 3.1 INTRODUCTION AND DRUG HISTORY

**NDA number:** 22-304

**Review number:** 1

**Sequence number 000 /** January 23, 2008 / Original New Drug Application

**Sequence number 0002 /** March 13, 2008 / Labeling Supplement

**Sequence number 0003 /** March 19, 2008 / Amendment to A pending Application:  
Nonclinical Carcinogenicity Datasets

**Sequence number 0004 /** April 7, 2008 / Amendment to A pending Application:

Response to Request for Information 27 March 2008 (Nonclinical Pharmacology and  
Toxicology Section: Mouse and Rat Carcinogenicity Study Datasets)

**Sequence number 0015 /** August 8, 2008 / Amendment to A pending Application:

Response to FDA Nonclinical Information Request of 04 August 2008

(Toxicokinetic/Pharmacokinetic Data on Doses for the Segment 1 Study in Wistar Rats

**Sequence number 0017 /** August 21, 2008 / Nonclinical Study Report: Mouse and Rat

**Sequence number 0019 BP /** September 5, 2008 / Amendment to A pending Application:

Response to FDA 26 August 2008 Nonclinical Request for Information (Rat and Mouse  
Tumor Data)

**Information to sponsor:** Yes ( ) No ( x)

**Sponsor and/or agent:** Ortho-McNeil Pharmaceutical, Inc.

**Manufacturer for drug substance:** Janssen Ortho, LLC, State Road 933, KM 0.1,  
Gurabo, PR 00778

**Reviewer name:** Kathleen Young, Ph.D.

**Division name:** Division of Anesthesia, Analgesia, and Rheumatology Products

**HFD #:** 170

**Review completion date:** September 12, 2008

#### Drug:

Trade name: None

Generic name: Tapentadol HCl

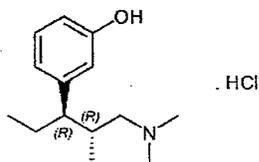
Code names: BN-200, BN 200, BN200, CG5503, R331333, JNJ-26120211-AAC

Chemical name: 3-[(1R,2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol

CAS registry number: 175591-09-0

Molecular formula/molecular weight: C<sub>14</sub>H<sub>23</sub>NO·HCl / 257.80

Structure:



**Relevant INDs/NDAs/DMFs:** IND 61,345

**Drug class:** Mu-Opioid receptor (MOR) agonist/norepinephrine (NE) re-uptake inhibitor

**Indication:** Treatment of moderate to severe acute pain

**Clinical formulation** (table provided from the original NDA submission):

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**Route of administration:** Oral

**Proposed use:** For the treatment of moderate to severe pain at 50, 75, or 100 mg every 4-6 hours, with one additional dose within 1 hour of the first dose on the first day of treatment, if needed. Total daily dose of up to 700 mg on Day 1, and 600 mg on subsequent days.

**Disclaimer:** The tabular and graphical information are taken from the original NDA submission, unless cited otherwise.

**Nonclinical Studies Conducted on Tapentadol (table provided from the original NDA submission):**

**Primary Pharmacodynamics**

Opioid receptor binding, Neurotransmitter uptake	Rat, brain synaptosomes	In vitro	Grünenthal, D	MP9
Opioid receptor binding	Rat, brain synaptosomes	In vitro	Grünenthal, D	MP14
[ <sup>35</sup> S]-GTPγS binding	CHO-K1 cells transfected with human μ-opioid receptor	In vitro	Grünenthal, D	MP29
Various other receptors <sup>a</sup>	Rat brain synaptosomes	In vitro	Grünenthal, D	MP30
Opioid agonism	Guinea pig, ileum	In vitro	Grünenthal, D	PH375
Microdialysis, central NA- and 5-HT levels	Rat, ventral hippocampus	i.p.	[ ]	PH613
Tail flick Test, low intensity	Rat, Sprague Dawley	i.th.	Grünenthal, D	PH374/A
Tail flick Test	Mouse, NMRI	i.v., p.o.	Grünenthal, D	PH378
Tail flick Test	Rat, Sprague Dawley	i.v., p.o.	Grünenthal, D	PH402
Tail flick Test	Dog, Beagle	i.v., p.o.	Grünenthal, D	PH524
Writhing Test, antagonism	Mouse, NMRI	i.v., p.o.	Grünenthal, D	PH380
Writhing Test, antagonism	Mouse, NMRI	i.v.	Grünenthal, D	PH600
Hot plate 48° C Test	Mouse, NMRI	i.v.	Grünenthal, D	PH384
Hot plate 58° C Test		i.p.		
Formalin Test	Rat, Sprague Dawley	i.p.	Grünenthal, D	PH386
Formalin Test, antagonism	Rat, Sprague Dawley	i.p.	Grünenthal, D	PH523
Randall Selitto Test (yeast), antagonism	Rat, Sprague Dawley	i.v.	Grünenthal, D	PH392
Randall Selitto Test (yeast)	Rat, Sprague Dawley	i.p., i.th.	Grünenthal, D	PH393
Tooth pulp Stimulation	Rabbit, New Zealand White	i.v.	Grünenthal, D	PH394
Spinal cord	Anesthetized rat, Sprague Dawley	i.v.	Grünenthal, D	PH395
Stimulated dorsal horn (NMDA, AMPA or heart)	Anesthetized rat, Wistar	i.v.	Grünenthal, D	PH417
Chronic constriction injury (CCI) (Bennett) (mononeuropathy)	Rat, Sprague Dawley	i.p.	Grünenthal, D	PH372
Spinal nerve ligation (SNL) (Chung) (mononeuropathy)	Rat, Sprague Dawley	i.p.	Grünenthal, D	PH438
Spinal nerve ligation (SNL), antagonism (Chung) (mononeuropathy)	Rat, Sprague Dawley	i.p.	Grünenthal, D	PH597
Diabetic Polyneuropathy, STZ-induced diabetes	Rat, Sprague Dawley	i.p.	Grünenthal, D	PH534
Cytostatic (vincristine)-induced polyneuropathy	Rat, Sprague Dawley	i.p.	Grünenthal, D	PH579
Mustard oil-induced visceral inflammation	Mouse, NMRI	i.v. - prophylactic i.v. - curative	Grünenthal, D	PH577
Colorectal distension	Rat, Sprague Dawley	i.v.	Grünenthal, D	PH578
Paw incision - primary hypersensitivity	Rat, Sprague Dawley	i.p.	Grünenthal, D	PH586
<b>Studies with metabolites</b>				
Various receptor binding	Rat, cerebral cortex, CHO Cells, HEK-293 cells, Sf9 cells, U-373 MG cells	In vitro	[ ]	MP23
Opioid receptor binding	Rat, brain synaptosomes	In vitro	Grünenthal, D	MP28
Tail flick	Mouse, NMRI	i.v., i.c.v.	Grünenthal, D	PH517/A
	Rat, not specified	i.v.		
Tail flick and writhing	Mouse, NMRI	i.v., i.c.v.	Grünenthal, D	PH628

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Hemodynamic and cardiac electrophysiologic effects <sup>a</sup>	Anesthetized dogs - Beagle	i.v.	[ ]	SP103/A	b(4)
Cardiovascular effects (QT-interval) <sup>b</sup>	Conscious dog - Beagle	i.v.	[ ]	SP35/A	
Aconitine-induced arrhythmia	Anesthetized mouse, NMRI	i.v.	Grünenthal, D	PH377	
Spontaneous respiratory rate	Rat, Wistar	i.v.	Grünenthal, D	PH389	
CO <sub>2</sub> -induced respiratory stimulation					
Plethysmography <sup>a</sup>	Rat, Wistar	i.v.	[ ]	SP140	b(4)
Blood gas analysis	Rat, Sprague Dawley	i.v.	Grünenthal, D	SP151	
Tolerance to respiratory depression	Rat, Sprague Dawley	i.p.	Grünenthal, D	SP177	
General toxicity	Rat, Wistar	i.v.	Grünenthal, D	SP142/A	
Charcoal transit	Mouse, NMRI	i.p.	Grünenthal, D	PH391	
PGE <sub>2</sub> -induced diarrhea	Mouse, NMRI	i.p.	Grünenthal, D	PH388	
Diuresis/saluresis	Rat, Wistar	i.v.	Grünenthal, D	PH387	
Acetylcholine antagonism	Guinea pig, isolated ileum	In vitro	Grünenthal, D	PH390	
Traction Test	Mouse, NMRI	i.v.	Grünenthal, D	SP166	
Ikr/HERG, metabolites	CHO cells	In vitro	[ ]	SP101	
Action potential, metabolite	Guinea pig, papillary muscle	In vitro	Grünenthal, D	SP144	b(4)
Ikr/HERG, metabolite	CHO cells	In vitro	[ ]	SP131	

**Pharmacodynamic Drug Interactions**

Hexobarbital (refer to hexobarbital sleep: PH385)  
 Muscle relaxants (refer to traction test: SP166)

Hemodynamic and cardiac electrophysiologic effects <sup>a</sup>	Anesthetized dogs - Beagle	i.v.	[ ]	SP103/A	b(4)
Cardiovascular effects (QT-interval) <sup>b</sup>	Conscious dog - Beagle	i.v.	[ ]	SP35/A	
Aconitine-induced arrhythmia	Anesthetized mouse, NMRI	i.v.	Grünenthal, D	PH377	
Spontaneous respiratory rate	Rat, Wistar	i.v.	Grünenthal, D	PH389	b(4)
CO <sub>2</sub> -induced respiratory stimulation					
Plethysmography <sup>a</sup>	Rat, Wistar	i.v.	[ ]	SP140	
Blood gas analysis	Rat, Sprague Dawley	i.v.	Grünenthal, D	SP151	
Tolerance to respiratory depression	Rat, Sprague Dawley	i.p.	Grünenthal, D	SP177	
General toxicity	Rat, Wistar	i.v.	Grünenthal, D	SP142/A	
Charcoal transit	Mouse, NMRI	i.p.	Grünenthal, D	PH391	
PGE <sub>2</sub> -induced diarrhea	Mouse, NMRI	i.p.	Grünenthal, D	PH388	
Diuresis/saluresis	Rat, Wistar	i.v.	Grünenthal, D	PH387	
Acetylcholine antagonism	Guinea pig, isolated ileum	In vitro	Grünenthal, D	PH390	
Traction Test	Mouse, NMRI	i.v.	Grünenthal, D	SP166	
Ikr/HERG, metabolites	CHO cells	In vitro	[ ]	SP101	
Action potential, metabolite	Guinea pig, papillary muscle	In vitro	Grünenthal, D	SP144	b(4)
Ikr/HERG, metabolite	CHO cells	In vitro	[ ]	SP131	

**Pharmacodynamic Drug Interactions**

Hexobarbital (refer to hexobarbital sleep: PH385)  
 Muscle relaxants (refer to traction test: SP166)

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Secondary Pharmacodynamics

Emesis	Ferret	i.p.		PH403/A
Antiemesis	Ferret	i.p.		PH527
Antitussive effect	Rat, Sprague Dawley	i.v.	Grünenthal, D	PH381
Local anaesthesia	Guinea pig, Pirbright white	intradermal	Grünenthal, D	PH382

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Safety Pharmacology

Hole board	Mouse, NMRI	i.p.	Grünenthal, D	PH383
Hexobarbital sleep	Mouse, NMRI	i.p.	Grünenthal, D	PH385
Rota rod	Mouse, CD-1	i.p.	Grünenthal, D	PH396
Irwin test <sup>a</sup>	Rat, Wistar	i.v.		SP138
Pentetrazole-induced convulsion <sup>a</sup>	Rat, Wistar	i.v.		SP139
General toxicity/prevention of convulsions	Rat, Sprague Dawley	i.v.	Grünenthal, D	TP2542
Prevention of convulsions by naloxon	Rat, Sprague Dawley	i.v.	Grünenthal, D	TP2966
IKr/HERG	CHO cells	In vitro		SP21
Action potential <sup>a</sup>	Rabbit, papillary muscle	In vitro		SP70
Action potential	Guinea pig, papillary muscle	In vitro	Grünenthal, D	SP122
Volume-conducted electrocardiogram	Guinea pig, Isolated perfused heart	In vitro	Grünenthal, D	SP154
Isolated atrium and papillary muscle	Guinea pig Pirbright white	In vitro	Grünenthal, D	PH379
Vascular tone effects	Rat, Isolated aortic strips	In vitro	Grünenthal, D	SP220
Blood pressure and heart rate	Conscious rat, Sprague Dawley	i.v.	Grünenthal, D	PH371
Cardiohaemodynamic and respiratory effects <sup>a</sup>	Rabbits, New Zealand White	i.v.	Grünenthal, D	PH323

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i.p. = intraperitoneal; i.c.v. = intracerebroventricular; i.th. = intrathecal; i.v. intravenous; p.o. = gavage

<sup>a</sup> - GLP compliant report

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**Absorption**

<i>In vitro</i> absorption	CACO-2 HCT-8	<i>in vitro</i>	-	39 $\mu$ M (8.6 $\mu$ g/mL)	No	PK744
Pharmacokinetics Single dose	Mouse, NMRI	i.v. p.o.	Single dose	8 80	No	PK689
Pharmacokinetics Single dose - Repeat dose	Rat, Wistar	p.o.	Single dose 7 days bid	300 300 (1 <sup>st</sup> day)/150 (from day 2 onwards) per administration	Yes	PK486/A
Pharmacokinetics Single dose Repeat dose	Dog, Beagle	p.o., i.v. p.o., i.v.	Single dose 7 days bid	100, 5 100, 5	Yes	PK483/A
Pharmacokinetics - Single dose	Rat, Sprague Dawley	i.v.	Single dose	3.5, 7, 14	No	PK653
Pharmacokinetics- Single dose Repeat dose	Rat, Wistar	i.v.	Single dose 7 days bid	7 7	Yes	PK485/A

**Distribution**

Protein binding	Mouse, rat, rabbit, dog, human	<i>In vitro</i>	-	0.05, 0.2, 0.8 $\mu$ g/mL	No	PK582
Brain penetration	Rat, (Sprague Dawley)	p.o.	6 doses	80	No	PK664
Tissue distribution	Rat, (Sprague Dawley and Lister Hooded)	i.v.	Single dose	10	Yes	PK432

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<b>Metabolism</b>						
<i>In vitro</i> glucuronidation	Human and rat liver	<i>In vitro</i>	-	221 µg/mL 22 - 133 µg/mL	No	PK528
<i>In vitro</i> metabolism	Hepatic microsomes	<i>In vitro</i>	-	2.2-133 µg/mL	No	PKN233/A
<i>In vivo</i> metabolism	Mouse, rat, rabbit, dog, human	p.o.	Single + repeated dosing	Different doses up to 300	No	PK581K/A
<b>Excretion</b>						
Mass balance	Mouse, NMRI	p.o.	Single dose	50	No	PK586/A
Mass balance	Rat, SD	p.o.	Single dose	150	No	PK583
Mass balance	Dog, Beagle	p.o.	Single dose	20	No	PK480/A
<b>Pharmacokinetic drug interactions</b>						
Induction potential for CYPs	Human hepatocytes	<i>In vitro</i>	-	0.7, 10, 100 µM (0.16, 2.2, 22 µg/mL)	No	PK679
Inhibition potential for CYPs	Human liver microsomes	<i>In vitro</i>	-	0.025 to 616 µM (0.006 to 136 µg/mL)	No	PK680
Co-medication and inhibition of glucuronidation	Human liver microsomes rUGTs	<i>In vitro</i>	-	Up to 221 µg/mL	No	PK681

<sup>a</sup> = Pregnant and non-pregnant SD rats,

rUGTs = recombinant UDP-glucuronyl transferase isoforms

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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			
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
Dependence			
withdrawal jumping	i.p. (2 studies)	mouse	no
conditioned place preference	i.p.	rat	no
Drug discrimination	i.p.	rat	no
tolerance and cross tolerance	i.p. (3 studies)	rat	no
Self administration	i.v.	monkey	no

**Studies reviewed within this submission:**

CG5503: 26-Week Oral Toxicity (Gavage) Study in the Rat (Study TP 2397)

CG5503 (BN200): 13-Week Oral (Gavage) Toxicity Study in the Dog (Study TP2415)

CG5503: 52-Week Oral (Gavage) Toxicity Study in the Dog (Study TP2441)

Pilot Study on the Toxicokinetics and the Toxicity of CG5503 After Repeated Intravenous and Oral Administrations to Cynomolgus Monkeys (Study TP2316)

Chromosome Aberration Assay in Chinese Hamster V79 Cells *in vitro* with BN 200 (Study TP 1976/95)

*Salmonella typhimurium* and *Escherichia coli* Reverse Mutation Assay with BN 200 (Study TP 1990/95)

*In vitro* Chromosome Aberration Test in Chinese Hamster V79 Cells with BN 200 (Study TP 2448)

Chromosome Aberration Assay in Bone Marrow Cells of the Rat with BN 200 (Study [redacted] 550300)

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*In vivo/In vitro* Unscheduled DNA Synthesis in Rat Hepatocytes with BN 200 (Study [redacted] 584900)

CG5503: 104 Week Oncogenicity (Feeding) Study in the Rat (Study TP2418)

CG5503: 104 Week Oral (Gavage) Administration Oncogenicity Study in the Mouse (Study TP2518)

14-Day Dose-Range-Finding Study to Determine the Dose Levels for an Examination of the Influence of CG5503 on the Pregnant Rat and the Fetus by Subcutaneous Administration Twice Daily (Study TP2465)

CG5503 Preliminary Study for Tolerability in Pregnant Rats by Twice Daily Oral (Gavage) Administration (Study TP2767)

CG5503: 14-Day Dose-Range-Finding Study to Determine the Dose Levels for an Examination of the Influence of BN-200 in the Pregnant Rabbit and the Fetus by Intravenous Administration (Study TP2061)

14-Day Dose-Range-Finding Study to Determine the Dose Levels for an Examination of the Influence of CG5503 on the Pregnant Rabbit and the Fetus by Subcutaneous Administration Twice Daily (Study TP2464)

CG5503: Study of Fertility and Early Embryonic Development to Implantation in the Rat (Study TP2445)

Examination of the Influence of BN-200 on the Pregnant Rat and the Fetuses by Intravenous Administration – Embryotoxicity Study (Study LTP 10434/97, TP2060)

Study of Embryo-Fetal Development in Rats with CG5503 (BN200) by Subcutaneous Administration (Study TP2510)

Examination of the Influence of BN-200 on the Pregnant Rabbit and the Fetus by Intravenous Administration – Embryotoxicity Study (Study TP 2062)

Study of Embryo-fetal Development in Rabbits with CG5503 (BN200) by Subcutaneous Administration (Study TP2511)

CG5503: Combined Preliminary Study for Effects on Pre- and Post-Natal Development and Juvenile Toxicity by Once/Twice Daily Oral (Gavage) Administration in Rats (Study TP2772)

CG5503: Study for Effects on Pre- and Post-Natal Development by Twice Daily Oral (Gavage) Administration to Rats (Study TP2834)

**Studies not reviewed within this submission:** Nonclinical studies not listed above were reviewed previously (IND 61,345) and/or are summarized within this review.

### 3.1 Introduction

Tapentadol is a centrally acting analgesic new molecular entity, that is being developed for the treatment of moderate to severe, acute and chronic pain at oral doses of 100 mg up to 6 times daily (600 mg/day), and up 7 times on the first day of treatment (700 mg). The Sponsor's rationale for development of this drug product is a potential for enhanced mu-opioid induced analgesic activity by interaction with norepinephrine transmission, with fewer adverse effects that are usually associated with treatment using more selective mu-agonist agents, such as morphine and fentanyl.

### 3.2 PHARMACOLOGY

#### 3.2.2 Primary pharmacodynamics

The results of *in vitro* receptor-, ion channel-, and neurotransmitter transporter-binding studies demonstrated affinity of tapentadol for the following target sites (in decreasing order of affinity): mu-opioid receptor, sigma2 (S2) receptor, norepinephrine uptake, muscarinic (M1) receptor, kappa-opioid receptor, delta-opioid receptor, serotonin (5HT3) receptor, N-methyl-D-aspartate (NMDA-PCP) receptor, sigma (S1) receptor, serotonin (5HT) uptake, L-type-Ca<sup>++</sup> channel and serotonin (5HT2) receptor. The primary target sites are the mu-opioid and sigma2 receptors, and the norepinephrine transporter.

Pharmacodynamic activity characteristic of opioid agonist effect was shown in an *ex vivo* assay, by inhibition of the twitch reaction in isolated guinea pig ileum that was reversed by the opioid antagonist naloxone. Tapentadol is also an antagonist at the muscarinic receptor. Potential neurotoxic effects by interaction with the NMDA receptor were investigated by the Sponsor (see summary under Section 3.4.8 Special toxicology studies, below).

Mechanism of action: The primary mechanism of action of tapentadol in the treatment of pain is believed to be due to mu-opioid receptor agonist effects in conjunction with norepinephrine reuptake inhibition, based on the results of the receptor binding and primary pharmacology studies in animals, and the treatment-related findings in the nonclinical studies that are consistent with those found by other drugs in these classes.

**Receptor Binding (Study MP30)**

The results of receptor-binding assays on tapentadol (here referred to as CG5503) and several other lead compounds by the Sponsor are presented in the following table (reproduced from the original NDA submission):

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*Table A: CRO Study Nr. # 983007*

<i>Target site (Binding assays)</i>	<i>Origin</i>	<i>Ligand</i>	<i>Result (CG5503) effect at 3µM</i>
Adenosine A <sub>1</sub>	rat cerebral cortex	[ <sup>3</sup> H]CCPA	< 10% inhibition
Adenosine A <sub>2A</sub>	human recombinant	[ <sup>3</sup> H]CGS 21680	< 10% inhibition
α <sub>1</sub> -adrenergic (non-selective)	rat cerebral cortex	[ <sup>3</sup> H]prazosin	< 10% inhibition
α <sub>2</sub> -adrenergic (non-selective)	rat cerebral cortex	[ <sup>3</sup> H]RX 821002	< 10% inhibition
β <sub>1</sub> -adrenergic	rat heart	[ <sup>3</sup> H](-)CGP 12177 + 10 nM ICI 118551	13% inhibition
NE transporter	rat cerebral cortex	[ <sup>3</sup> H]nisoxetine	49% inhibition
Angiotensin AT <sub>1</sub>	rat lung	[ <sup>3</sup> H]angiotensin II	< 10% inhibition
Benzodiazepine BZD (central)	rat cerebral cortex	[ <sup>3</sup> H]flunitrazepam	< 10% inhibition
Bradykinin B <sub>2</sub>	human recombinant	[ <sup>3</sup> H]bradykinin	< 10% inhibition
Cholecystokinin CCK <sub>A</sub> (CCK <sub>1</sub> )	rat pancreas	[ <sup>125</sup> I]CCK-8	< 10% inhibition
Dopamine D <sub>1</sub>	rat striatum	[ <sup>3</sup> H]SCH 23390	< 10% inhibition
Dopamine D <sub>2</sub>	rat striatum	[ <sup>3</sup> H]YM-09151-2	< 10% inhibition
DA transporter	rat striatum	[ <sup>3</sup> H]BTCP	< 10% inhibition
Endothelin ET <sub>A</sub>	human recombinant	[ <sup>125</sup> I]endothelin-1	< 10% inhibition
GABA (non-selective)	rat cerebral cortex	[ <sup>3</sup> H]GABA	< 10% inhibition
Glutamate NMDA	rat cerebral cortex	[ <sup>3</sup> H]CGP 39653	< 10% inhibition
Histamine H <sub>1</sub> (central)	guinea-pig cerebellum	[ <sup>3</sup> H]pyrilamine	< 10% inhibition
Muscarinic M (non- selective)	rat cerebral cortex	[ <sup>3</sup> H]QNB	82% inhibition
Neurokinin NK <sub>1</sub>	U-373MG cells (human)	[ <sup>3</sup> H][Sar <sup>9</sup> ,Met(O <sub>2</sub> ) <sup>11</sup> ]- SP	< 10% inhibition
Neuropeptide Y (non- selective)	rat cerebral cortex	[ <sup>3</sup> H]NPY	< 10% inhibition
Nicotinic N (neuronal) (α-BGTX-insensitive) (α4β2)	rat cerebral cortex	[ <sup>3</sup> H]cytisine	< 10% inhibition
Opioid (non-selective)	rat cerebral cortex	[ <sup>3</sup> H]naloxone	91% inhibition
Glutamate PCP	rat cerebral cortex	[ <sup>3</sup> H]TCP	32% inhibition
Serotonin 5-HT (non- selective)	rat cerebral cortex	[ <sup>3</sup> H]serotonin	20% inhibition
Serotonin 5-HT <sub>1B</sub>	rat cerebral cortex	[ <sup>125</sup> I]CYP	< 10% inhibition
Serotonin 5-HT <sub>2A</sub>	rat cerebral cortex	[ <sup>3</sup> H]ketanserin	12% inhibition
5-HT transporter	rat cerebral cortex	[ <sup>3</sup> H]paroxetine	38% inhibition

*Continued* **Table A: CRO [ ] Study Nr. # 983007**

<i>Target site (Binding assays)</i>	<i>Origin</i>	<i>Ligand</i>	<i>Result (CG5503) effect at 3µM</i>
Sigma σ (non-selective)	rat cerebral cortex	[ <sup>3</sup> H]DTG	65% inhibition
Glucocorticoid receptor (GR)	L-929 cells cytosol (mouse)	[ <sup>3</sup> H]triamcinolone	< 10% inhibition
Vasopressin V <sub>1</sub>	A7r5 cells (rat)	[ <sup>3</sup> H]AVP	< 10% inhibition

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**Table B: CRO [ ] Study Nr. # 6192**

<i>Target site (Enzyme assays)</i>	<i>Origin</i>	<i>Substrate (Stimulus)</i>	<i>Result (CG5503) effect at 3µM</i>
Cyclooxygenase COX <sub>1</sub>	human platelets	arachidonic acid (4 µM)	23% stimulation
Cyclooxygenase COX <sub>2</sub> (whole cell-activity)	HUV-EC-C cells (human)	arachidonic acid (50 µM) Stimulus : PMA (100 nM)	13% stimulation

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<i>Table C: CROC Study Nr. # 983020</i>			
<i>Target site (Bioassay)</i>	<i>Tissue</i>	<i>Reference agonist</i>	<i>Reference antagonist</i>
Serotonin 5-HT <sub>3</sub>	guinea-pig colon	Serotonin	MDL 72222

<i>Table C a: Test for agonist activity</i>				
Compounds	Responses to increasing concentrations of the compounds			+ MDL 72222 (30 µM)
	3 µM	10 µM	30 µM	
BN 200	0 %	0 %	0 %	not tested
	1 µM	3 µM	10 µM	10 µM
serotonin	27 %	74 %	95 %	0 %

<i>Table C b: Test for antagonist activity</i>				
Compounds	Responses to serotonin (10 µM) in the presence of increasing concentrations of the compounds			
	3 µM	10 µM	30 µM	
BN 200	63 %	31 %	19 %	
	0,3 µM	3 µM	30 µM	
MDL 72222	91 %	31 %	0 %	

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Effects of the test compounds on the specific radioligand binding to the receptors studied and IC<sub>50</sub> values for the reference compounds

Receptors	CG 5503	GRT0102B	GRT1864G	Reference compounds		
	3x10 <sup>-8</sup> M	3x10 <sup>-8</sup> M	3x10 <sup>-8</sup> M		IC <sub>50</sub> (x10 <sup>-9</sup> M)	(nH)
A <sub>1</sub>	-	-	-	CPA	0.91	(1.0)
A <sub>2A</sub> (h)	-	-	-	NECA	89	(0.8)
α <sub>1</sub> (non-selective)	-	-	-	prazosin	1.2	(1.4)
α <sub>2</sub> (non-selective)	-	-	39	yohimbine	78	(1.0)
β <sub>1</sub>	13	-	19	atenolol	659	(0.8)
NE uptake	49	46	27	protriptyline	5.7	(1.9)
AT <sub>1</sub>	-	12	12	saralasin	0.96	(1.3)
BZD (central)	-	-	11	diazepam	12	(1.2)
B <sub>2</sub> (h)	-	-	-	NPC 567	5.8	(0.9)
CCK <sub>A</sub> (CCK <sub>1</sub> )	-	-	-	CCK-8	0.51	(1.1)
D <sub>1</sub>	-	-	-	SCH 23390	0.82	(1.0)
D <sub>2</sub>	-	-	12	(-)-butaclamol	12	(1.1)
DA uptake	-	-	69	nomifensine	120	(0.9)
ET <sub>A</sub> (h)	-	-	-	endothelin-1	0.14	(1.1)
GABA (non-selective)	-	-	-	GABA	69	(0.9)
NMDA	-	-	-	CGS 19755	715	(0.9)
H <sub>1</sub> (central)	-	-	11	pyrilamine	3.6	(1.1)
M (non-selective)	82	-	45	atropine	0.93	(1.2)
NK <sub>1</sub> (h)	-	-	11	[Sar <sup>9</sup> ,Met(O <sub>2</sub> ) <sup>11</sup> ]-SP	5.4/2.0	(0.9/0.8)
Y (non-selective)	-	-	-	NPY	1.5	(0.7)
N (neuronal)	-	-	-	nicotine	13/11	(1.4/1.1)
Opiate (non-selective)	91	28	94	naloxone	1.3	(1.2)
PCP	32	10	60	MK 801	12	(1.1)
5-HT (non-selective)	20	-	-	serotonin	1.7	(0.9)
5-HT <sub>1B</sub>	-	-	12	serotonin	33	(0.8)
5-HT <sub>2A</sub>	12	-	29	ketanserin	1.8	(0.8)
5-HT uptake	38	16	-	zimelidone	138	(1.1)
σ (non-selective)	65	18	95	haloperidol	81	(0.8)
Glucocorticoid	-	-	-	dexamethasone	133	(0.9)
V <sub>1</sub>	-	-	16	V <sub>1</sub> -antagonist	0.55	(0.8)

For the test compounds, the results are expressed as a percent inhibition of control specific binding (mean values ; n = 2).  
The symbol - indicates an inhibition of less than 10%.

Receptors	compounds $3 \times 10^{-8}$ M	% control specific binding		
		1 <sup>st</sup> value	2 <sup>nd</sup> value	mean
A <sub>1</sub>	CG 5503	105.3	109.0	107.1
	GRT0102B	98.0	107.8	102.9
	GRT1864G	91.4	114.8	103.1
A <sub>2A</sub> ( <i>h</i> )	CG 5503	98.0	98.2	98.1
	GRT0102B	94.0	95.3	94.7
	GRT1864G	99.9	96.0	98.0
$\alpha_1$ (non-selective)	CG 5503	98.4	96.4	97.4
	GRT0102B	103.2	108.4	105.8
	GRT1864G	91.2	98.0	94.6
$\alpha_2$ (non-selective)	CG 5503	111.1	116.2	113.7
	GRT0102B	118.5	97.8	108.2
	GRT1864G	57.4	64.6	61.0
$\beta_1$	CG 5503	80.2	94.3	87.2
	GRT0102B	96.6	87.5	92.1
	GRT1864G	84.7	76.7	80.7
NE uptake	CG 5503	53.5	47.7	50.6
	GRT0102B	57.8	49.3	53.5
	GRT1864G	68.0	78.4	73.2
AT <sub>1</sub>	CG 5503	104.5	84.0	94.2
	GRT0102B	81.2	94.1	87.7
	GRT1864G	84.8	91.6	88.2
BZD (central)	CG 5503	95.2	86.1	90.7
	GRT0102B	90.8	102.4	96.6
	GRT1864G	91.5	86.7	89.1
B <sub>2</sub> ( <i>h</i> )	CG 5503	98.0	95.9	96.9
	GRT0102B	95.2	91.7	93.5
	GRT1864G	90.5	97.8	94.1
CCK <sub>A</sub> (CCK <sub>1</sub> )	CG 5503	112.0	133.6	122.8
	GRT0102B	127.4	124.3	125.9
	GRT1864G	117.7	91.9	104.8
D1	CG 5503	92.1	98.5	95.3
	GRT0102B	89.3	105.2	97.3
	GRT1864G	94.3	96.9	95.6
D2	CG 5503	106.4	97.6	102.0
	GRT0102B	99.1	112.0	105.6
	GRT1864G	95.2	80.0	87.6
DA uptake	CG 5503	94.4	97.9	96.2
	GRT0102B	95.0	99.9	97.4
	GRT1864G	27.4	34.0	30.7

Receptors	compounds 3x10 <sup>-6</sup> M	% control specific binding		
		1 <sup>st</sup> value	2 <sup>nd</sup> value	mean
ET <sub>A</sub> (h)	CG 5503	96.4	88.2	92.3
	GRT0102B	113.4	102.3	107.8
	GRT1864G	130.4	93.5	112.0
GABA (non-selective)	CG 5503	112.6	131.9	122.3
	GRT0102B	125.8	123.3	124.5
	GRT1864G	120.9	108.6	114.8
NMDA	CG 5503	102.4	98.7	100.6
	GRT0102B	97.9	97.5	97.7
	GRT1864G	101.5	92.9	97.2
H <sub>1</sub> (central)	CG 5503	94.2	93.1	93.7
	GRT0102B	108.7	101.4	105.1
	GRT1864G	98.6	80.2	89.4
M (non-selective)	CG 5503	18.7	18.3	18.5
	GRT0102B	98.1	89.2	93.6
	GRT1864G	53.0	56.5	54.7
NK <sub>1</sub> (h)	CG 5503	94.4	90.9	92.6
	GRT0102B	99.2	107.1	103.2
	GRT1864G	79.1	99.4	89.3
Y (non-selective)	CG 5503	96.9	123.7	110.3
	GRT0102B	100.3	88.0	94.1
	GRT1864G	99.8	105.4	102.6
N (neuronal)	CG 5503	111.1	113.1	112.1
	GRT0102B	91.2	94.7	92.9
	GRT1864G	100.7	108.4	104.5
Opiate (non-selective)	CG 5503	11.7	6.3	9.0
	GRT0102B	76.3	66.9	71.6
	GRT1864G	7.5	5.2	6.4
PCP	CG 5503	69.6	67.3	68.5
	GRT0102B	86.1	93.9	90.0
	GRT1864G	43.0	37.6	40.3
5-HT (non-selective)	CG 5503	72.4	87.6	80.0
	GRT0102B	116.7	108.4	112.6
	GRT1864G	114.8	106.7	110.8
5-HT <sub>1B</sub>	CG 5503	103.1	116.3	109.7
	GRT0102B	111.2	91.9	101.6
	GRT1864G	91.7	83.7	87.7
5-HT <sub>2A</sub>	CG 5503	87.0	88.2	87.6
	GRT0102B	91.1	103.1	97.1
	GRT1864G	72.4	69.0	70.7

Receptors	compounds 3x10 <sup>-6</sup> M	% control specific binding		
		1 <sup>st</sup> value	2 <sup>nd</sup> value	mean
5-HT uptake	CG 5503	59.6	64.1	61.9
	GRT0102B	84.4	83.2	83.8
	GRT1864G	106.7	81.0	93.8
σ (non-selective)	CG 5503	33.9	35.7	34.8
	GRT0102B	85.1	78.7	81.9
	GRT1864G	6.7	3.5	5.1
Glucocorticoid	CG 5503	99.1	99.2	99.1
	GRT0102B	102.2	100.8	101.5
	GRT1864G	103.7	102.4	103.1
V <sub>1</sub>	CG 5503	99.5	86.7	93.1
	GRT0102B	98.2	92.7	95.4
	GRT1864G	85.5	83.0	84.3

*In vivo* evaluations of tapentadol analgesic activity were conducted in models of acute antinociception and in inflammatory and neuropathic pain models. The results of the acute analgesia studies on tapentadol in mice, rats, and rabbits are presented in the following tables (provided from the original NDA submission):

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Test	Species	Test Article	ED50 (mg/kg)	Oral Activity	Time to 50% loss of effect
Tail-flick Test	Mouse	CG5503	4.22 IV 53.4 PO	8%	60 min 60 min
		Morphine	1.44 IV 26.1 PO	8%	90 min 110 min
		Tramadol	13.7 IV 23.8 PO	58%	80 min 180 min
Phenylquinone Writhing Test	Mouse	CG5503	0.66 IV 31.3 PO	2%	Not described
		Morphine	0.37 IV 4.70 PO	8%	
		Tramadol	3.59 IV 4.52 PO	80%	

Tail-flick Test	Rat	CG5503	2.24 IV 121 PO	2%	30 min 90 min
		Tramadol	9.63 IV 16.6 PO	58%	130 min 180 min
		Morphine	1.09 IV 55.7 PO	2%	50 min 420 min
Hot-plate Test (48°C)	Mouse	CG5503	3.25 IV 11.8 IP	Not applicable	Not described
		Tramadol	10.4 IV 20.7 IP		
		Morphine	1.33 IV 4.73 IP		
Hot-plate Test (58°C)	Mouse	CG5503	27.7 IP	Not applicable	Not described
		Tramadol Morphine	28.7 IP 8.51 IP		
Tooth Pulp Stimulation Test	Rabbit	CG5503	2.15-4.64 IV	Not described	Not described
		Morphine	2.28 IV		
		Tramadol	14.0 IV		

The efficacy of tapentadol antinociception by intrathecal injection was demonstrated by a significant increase in tail withdrawal latency in the tail-flick test in rats, with maximum effect noted at 20 minutes after dosing and a duration of action of 60 minutes.

The results of studies in several animal models of inflammatory and neuropathic pain are presented in the following table (provided from the original NDA submission):

APPEARS THIS WAY  
ON ORIGINAL

Test	Species	Test Article	ED50 (mg/kg)
Paw-pressure Test (inflammatory pain)	Rat	CG5503	1.98 IV 10.1 IP
		Morphine	56.8 IT (mcg/kg) 0.91 IV 5.59 IP
		Tramadol	1.85 IT (mcg/kg) 9.33 IV 8.58 IP 175 IT (mcg/kg)
Formalin Test (inflammatory pain)	Rat	CG5503	4.65-10.0 IP (1st phase) 3.75 IP (2nd phase)
		Morphine	4.50 IP (1st phase) 0.802 IP (2nd phase)
Chronic Constriction Injury Model (mononeuropathy)	Rat	CG5503	13 IP
		Tramadol	13.8 IP
		Morphine	7.1 IP

Naloxone partially blocked the acute antinociceptive effects of intravenous and oral tapentadol and tramadol in the phenylquinone writhing tests in mice. The antinociceptive effects of tapentadol in the paw-pressure test in rat, a model of inflammatory pain, was also blocked by naloxone, but not by the alpha2-receptor antagonist yohimbine and the serotonin-2A-C antagonist ritanserin.

### 3.2.3 Secondary pharmacodynamics

Tapentadol secondary pharmacodynamic effects were characterized in several experiments in rats and ferrets, and were found to be consistent with secondary pharmacodynamic findings generally characteristic of class effects by mu-opioid receptor agonist drugs. Intraperitoneal (IP) tapentadol was weakly emetic (inducing retching and/or vomiting in 20%-30% animals/dose at 10-31.6 mg/kg, compared to 100% by morphine at 0.125-0.5 mg/kg SC) in ferrets (Study PH403/A). However, IP tapentadol administered to ferrets at 10-21.5 mg/kg reduced the emetic effects of morphine and cisplatin (Study PH527). Retching and vomiting were commonly observed in the repeated dose toxicology studies in Beagle dogs given tapentadol by oral gavage for durations ranging from 2 weeks (50-150 mg/kg/d PO, Study TP1993) to 52 weeks (at doses of  $\geq 30$  mg/kg/day PO, Study TP2441). Treatment-related emesis cannot be demonstrated in rats. Antitussive effects were produced by intravenous (IV) tapentadol at doses of 0.215-2.15 mg/kg in Sprague Dawley rats, indicated by potent, dose-dependent inhibition of NH<sub>3</sub>-induced cough (ED<sub>50</sub> = 0.9 mg/kg, compared to 6.7 mg/kg by codeine phosphate, Study PH381). Local, intradermal injections at concentrations ranging from 0.05% to 0.5% in guinea pigs, resulted in inhibition of dermal twitch response to mechanical stimuli (EC<sub>50</sub> = 0.1%, Study PH382). In that study, the number of mechanical stimuli needed to elicit skin twitch was increased in a concentration-dependent manner.

### 3.2.4 Safety pharmacology

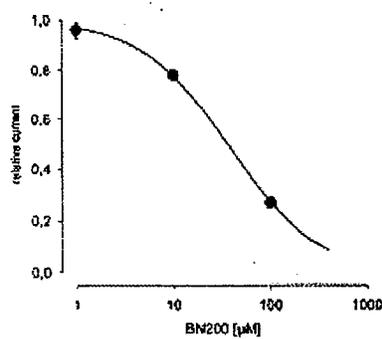
Neurological effects: Central nervous system (CNS) safety pharmacology studies on tapentadol were conducted in mice and rats. NMRI mice given single tapentadol doses by the intraperitoneal (IP) route showed dose-related decreased exploration activity in the Hole-Board test (12.5-46.4 mg/kg, ED<sub>50</sub> = 36.4 mg/kg vs. ED<sub>50</sub> by morphine = 23.6 mg/kg, Study PH383), and barbiturate anesthesia and dose-dependent (21.5-100 mg/kg) prolonged hexobarbital sleeping time (ED<sub>200</sub> = 71.2 mg/kg, Study PH385). Although tapentadol, given by IP injections of 21.5-100 mg/kg in CD-1 mice had no effects on motor coordination at doses of up to 46.4 mg/kg in the Rota Rod test, there was a transient reduction of time on the rotating rod of approximately 30 minutes (from 120 to 85 seconds) at 100 mg/kg (ED<sub>50</sub> = >100 mg/kg IP). In comparison, diazepam dose-dependently reduced the time on the rotating rod to 6 seconds (ED<sub>50</sub> = 9.2 mg/kg) in that study (Study TP396).

Conscious Wistar rats were administered intravenous (IV) tapentadol at single doses of 0 (vehicle) or 2-18 mg/kg in a standard Irwin test that included body temperature assessments (Study SP138). Mydriasis, exophthalmus, increased muscle tone, and insensitivity to tail pinch were observed at doses of 6 mg/kg and above, and decreased awareness, increased excitability, and loss of reflexes including corneal, pinna and hindlimb were observed at the high dose (HD). Clonic convulsions were seen in one of 8 HD male rats. Tapentadol was pro-convulsant, typical of opioid receptor agonist agents, in conscious male Wistar rats pre-treated with single IV doses from 0.6-18 mg/kg, prior to intraperitoneal (IP) pentylenetetrazole injection (PTZ, 40 mg/kg, 2/10, 0/10, 6/10, 8/10, and 9/9 at 0, 0.6, 2, 6, and 18 mg/kg tapentadol, respectively, Study SP139). One HD male died soon after tapentadol treatment, in that study. Convulsions were also observed in two studies in Sprague-Dawley rats administered single IV tapentadol at doses from 21.5-46.4 mg/kg. Tapentadol-induced convulsions observed in Study TP2542 were prevented by pre-treatment with diazepam (effective against all doses) and phenobarbital (effective at up to 31.6 mg/kg IV tapentadol), but not by naloxone (10 mg/kg IP). Naloxone dose-dependently (0.03-3.0 mg/kg IV) reduced the incidence of convulsions and Straub tail induced by tapentadol at 31.5 mg/kg IV (single dose), and abolished these neurological effects at the highest dose of 3 mg/kg IV in the second study in Sprague-Dawley rats (Study TP2966).

The results of a CNS Safety Pharmacology study conducted in rat to explore the timecourse of tapentadol-induced respiratory depression, convulsions and deaths in relation to plasma and CSF parent drug, O-glucuronide and sulfate metabolite concentrations showed treatment-related respiratory depression, cyanosis and convulsions starting 15-20 minutes after infusion, and also late peaks in the incidences of convulsions with cyanosis and deaths at ≥12 hours after dosing, and after parent drug and glucuronide metabolite were nearly completely cleared from plasma and CSF (below level of detection). Therefore, the late convulsions, cyanosis and deaths could not be attributed to plasma and CSF parent or glucuronide and sulfate metabolite concentrations. 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.

**Cardiovascular effects:** Studies on tapentadol cardiovascular safety were conducted in *in vitro*, *ex vivo* and *in vivo* assays. The results of a hERG assay (Study SP21) in Chinese Hamster Ovary cells transfected with human *ether-a-go-go* related gene treated at concentrations of 0 (vehicle) or 1-100 mcM tapentadol (referred to as BN200 in that study, dissolved in distilled water) showed reduction of the outward potassium tail current amplitudes at all concentrations (-4%, -22%, and -73%, at 1, 10, and 100 mcM, respectively). The IC<sub>50</sub> in this assay was  $36.14 \pm 1.51$  mcM ( $7978 \pm 332$  mcg/L), with 66% recovery after wash-out indicating partial reversibility. The results are presented in the following figure (provided from the original NDA submission):

**Concentration-Response for BN200 hERG Channel Blockade**



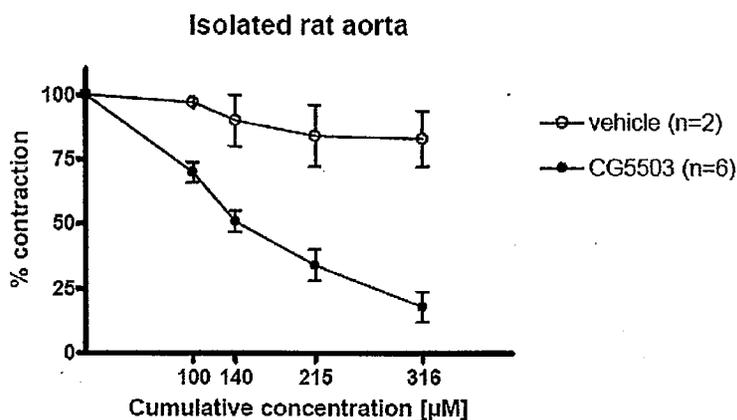
Tapentadol showed negative chronotropic effects in isolated guinea pig atrial muscle preparations at concentrations of 215-1000 mcM in a concentration-dependent manner (EC<sub>50</sub> = 408 mcM). In electrically driven, isolated Guinea pig papillary muscle (Study SP379), tapentadol reversed the positive inotropic effects (+19%) at 316 mcM and negative inotropic effects at higher concentrations of 383-681 mcM (EC<sub>50</sub> = 508 mcM). In comparison, the EC<sub>50</sub> in these preparations for quinidine sulfate negative chronotropic effects was 120 mcM and for the negative inotropic effects was 80 mcM. There were no effects on action potential parameters in isolated New Zealand White rabbit papillary muscles at concentrations of 3-10 mcM (in sterile water) under stimulation rates of 60 ppm and 6 ppm; however, action potential duration (APD<sub>90</sub>) was prolonged at 30 (6630 mcg/L, +22 ms at 1Hz, +17 ms at 0.1Hz) and 100 (22100 mcg/L, +49 ms at 1Hz, +65 ms at 0.1Hz) mcM in a dose-dependent manner, at 30%, 50%, 70%, and 90% repolarization (APD<sub>30</sub>, APD<sub>50</sub>, APD<sub>70</sub> and APD<sub>90</sub>, respectively, statistically significant at 100 mcM, EC<sub>50</sub> = >100 mcM, Study SP70).

There were no effects by tapentadol (referred to as CG5503 in that study) on action potential duration, upstroke velocity, action potential amplitude, resting membrane potential and contractile activity in isolated Guinea pig papillary muscles at concentrations of 0 (vehicle) or 0.1-1 mcM using stimulation frequencies of 0.5 Hz and 1

Hz (Study SP122). However, the action potential (APD90) was shortened at 10 (-3%, corresponding to 2600 ng/ml) and 100 (-9%, 26,000 ng/ml) mcM, and upstroke velocity (Vmax) and action potential amplitude (APA) were reduced at 100 mcM (up to 130 times the therapeutic plasma concentration at the clinical dose of 100 mg PO and 40 mg IV) in that study.

The effects of tapentadol (referred to as CG5503, 1-30 mcM, corresponding to 260-7800 ng/ml) on volume-conducted electrocardiogram were tested in isolated, spontaneously beating Guinea-Pig hearts (Langendorff heart preparations, Study SP154). There was a concentration-dependent reduction of heart rate at 3-30 mcM (corresponding to 663-6630 mcg/L, up to -30%), with atrio-ventricular conduction and ventricular depolarization slowing, indicated by reversible increase in PR interval (up to 22%) and QRS width broadening (up to 31%). No effects on QTc interval were observed in that study, at any concentration tested (vs. prolonged QTc interval by the positive control article dofetilide at 10 nM).

Tapentadol effects on vascular activity were investigated in isolated Sprague Dawley thoracic aortic strips bathed in tapentadol solutions (0.9% NaCl) at concentrations of 0 (vehicle), 100, 147, 215, and 316 mcM (tapentadol referred to as CG5503, Study SP220). Sodium channels were blocked by lidocaine. The results showed a concentration-dependent inhibition of calcium-dependent isometric aortic contractions in potassium-depolarized solution (IC50 = 153 mcM (corresponding to 33,813 ng/ml free base). The results of that study are presented in the following figure (provided from the original NDA submission):



**Figure 1:** Concentration-dependent reduction of rat aortic contractions by CG5503. Contractions were induced by addition of CaCl<sub>2</sub> (4.64 mM) in K<sup>+</sup>-depolarised solution in the presence of lidocaine (3 mM). Data as means ± SEM.

Tapentadol cardiovascular effects were studied *in vivo* in mice, rats, rabbits and dogs. Tapentadol (referred to as BN 200 in this study) was antiarrhythmic in aconitine-induced arrhythmias in mice, with a potency slightly less than that of quinidine sulfate. A dose-dependent increase in ventricular arrhythmogenic aconitine dose (aconitine infusion rate 0.25 mcg/min, arrhythmogenic aconitine dose increased from 64.6 to 81.9 mcg/kg IV) was observed in urethane-anesthetized male NMRI mice pretreated with IV tapentadol at doses of 4.64-21.5 mg/kg (in 0.9% NaCl solution, Study PH377). The ED50 for antiarrhythmic activity by tapentadol in this study was 10.6 mg/kg IV, vs. ED50 = 7.3 mg/kg IV for the positive control, quinidine sulfate.

Increases in heart rate (from 349 to 448 bpm at 10 mg/kg and from 381 to 460 bpm at 14.68 mg/kg) and systolic, diastolic, and mean (from 102 to 124 mmHg at 10 mg/kg and from 109 to 137 mmHg at 14.68 mg/kg) arterial blood pressures were observed in conscious, male Sprague-Dawley rats administered IV tapentadol doses of 0 (vehicle) or 4.64-14.6 mg/kg (NOEL = 4.64 mg/kg IV, Study PH371). In that study, blood pressure was increased, and heart rate initially decreased (from 381 to 294 bpm) and then increased (from 381 to 460 bpm) at 14.68 mg/kg IV. There were no effects by tapentadol at 4.64 mg/kg IV.

A study on tapentadol cardiohemodynamic and respiratory effects (referred to as BN200, Study PH323) was conducted in anesthetized New Zealand White rabbits given bolus IV bolus doses of 0 (vehicle) or 1-10 mg/kg (in saline solution, up to 3 times the ED50 for efficacy in tooth pulp analgesia in rabbits). The measures were recorded for 1 hour after injection. The results showed decreased cardiac contractility (-14%) and increased central venous pressure (+2.7 mmHg) at 1 mg/kg. Tapentadol decreased systolic (-14% and -42% at 4.64 and 10 mg/kg, respectively), diastolic (-23% and -52% at 4.64 and 10 mg/kg, respectively) and mean (-20% and -47% at 4.64 and 10 mg/kg, respectively) arterial blood pressures, starting during the injection and lasting for approximately 1 minute. Heart rate was decreased during the period from 10 to 60 minutes after injection (up to -16%) at these doses. Additionally, tapentadol reduced stroke volume and cardiac output for 60 minutes (-23% at 10 mg/kg). Increased central venous pressure (+1.6 and +3.4 mmHg at 4.64 and 10 mg/kg) and left ventricular end diastolic pressure (+ 1.8 and +4.8 mmHg) were observed at these doses, respectively, whereas treatment-related reductions in left ventricular systolic peak pressure (-10% and -36%, recovery by 1-2 minutes after dosing) and left ventricular contractility (-30% and -64%, respectively, recovery by 5 minutes after dosing) were observed. The ECG measurements showed reduced, eliminated or negative T-waves at 4.64 and 10 mg/kg, and prolonged PQ time (+10%), QRS time (+14% and +19% at these doses, respectively) lasting 2 minutes after injection, and prolonged S<sub>c</sub>T time (+22%). The results of this study are presented in the following tables (effect durations are presented in parentheses, tables provided from the original NDA submission):

#### **Cardiovascular Effects of Single Dose IV Tapentadol in Anesthetized Rabbits**

Parameter	1.0 mg/kg IV CG5503	4.64 mg/kg IV CG5503	10 mg/kg IV CG5503
Systolic Blood Pressure	No Effect	-14% (1 min)	-42% (1 min)
Diastolic Blood Pressure	No Effect	-23% (1 min)	-52% (1 min)
Mean Blood Pressure	No Effect	-20% (1 min)	-47% (1 min)
Heart Rate	No Effect	+16% (10-60 min)	+16% (10-60 min)
Cardiac Output (CO)	No Effect	<Vehicle controls	-23% (60 min)
Stroke Volume	No Effect	Similar to CO effects	Similar to CO effects
Central Venous Pressure	+2.7 mmHg	+1.6 mmHg	+3.4 mmHg
Left Ventricular End Diastolic Pressure	No Effect	+1.8 mmHg	+4.8 mmHg
Left Ventricular Systolic Peak Pressure	No Effect	-19% (1-2 min)	-36% (1-2 min)

Parameter	1.0 mg/kg IV CG5503	4.64 mg/kg IV CG5503	10 mg/kg IV CG5503
Left Ventricular Contractility	-14% (during,immed after dosing)	-30% (during,immed after dosing), -20% (1 h)	-64% (during,immed after dosing), -25% (1h)
Pulmonary Artery Pressure	No Effect	No Effect	No Effect
Femoral Artery Blood Flow	No Effect	No Effect	No Effect
Total Peripheral Artery Resistance	No Effect	No Effect	No Effect
Pulmonary Artery Resistance	No Effect	No Effect	No Effect
ECG Times/Parameters			
T-wave	No Effect	Reduced/Disappeared/Neg	Reduced/Disappeared/Neg
PQ Time	No Effect	Prolonged 10%	Prolonged 10%
QT Interval	No Effect	No Effect	No Effect
QRS Time	No Effect	+14% (2 min)	+19% (2 min)
SaT time	No Effect	+22%	No Effect

Conscious male Beagle dogs were administered tapentadol (dissolved in 0.9% NaCl solution) by short-term IV infusion (5 minutes) at doses of 0, 3, 6, and 9 mg/kg, and cardiovascular parameters were measured with particular attention to the potential effects on QT-interval (Study SP35A). There was a reversible, dose-related increase in arterial blood pressure (up to +43% at 9 mg/kg) and increased heart rate (up to +77% at  $\geq 3$  mg/kg) lasting approximately 30 minutes, increased cardiac output (at  $\geq 3$  mg/kg), and decreased left ventricular ejection fraction (at  $\geq 6$  mg/kg). The PQ interval was shortened at the highest dose administered, and the QT interval was decreased at all doses for up to 30 minutes after initiation of the infusion. There were no effects on stroke volume and QRS complex. The treatment-related effects on blood pressure were reversible by 60 minutes after the start of infusion. The serum concentrations were 665, 1105, and 2531 ng/ml at 3, 6, and 9 mg/kg IV, respectively.

In anesthetized male and female Beagle dogs (Study SP103A), 15-minute IV tapentadol (referred to as BN 200 in this study) infusions at doses of 0 (vehicle) or 0.5-4.5 mg/kg (in isotonic sodium chloride) produced dose-related cardiac depression that resulted in decreased blood pressures (systolic arterial pressure reduced 10% at 20 minutes after initiation of infusion at 1.5 mg/kg and reduced 16% at 15 minutes after start of infusion at 4.5 mg/kg) with associated peripheral arterial vasoconstriction. There were decreases in systolic left ventricular pressure (LVP), dLVP(+), dLVP(-), left ventricular work, cardiac output and stroke volume, that were statistically significant at the highest dose tested. A compensatory increase in total peripheral resistance was observed, indicating peripheral vasoconstriction. Reduced renal resistance and renal blood flow (-17% at 15 minutes

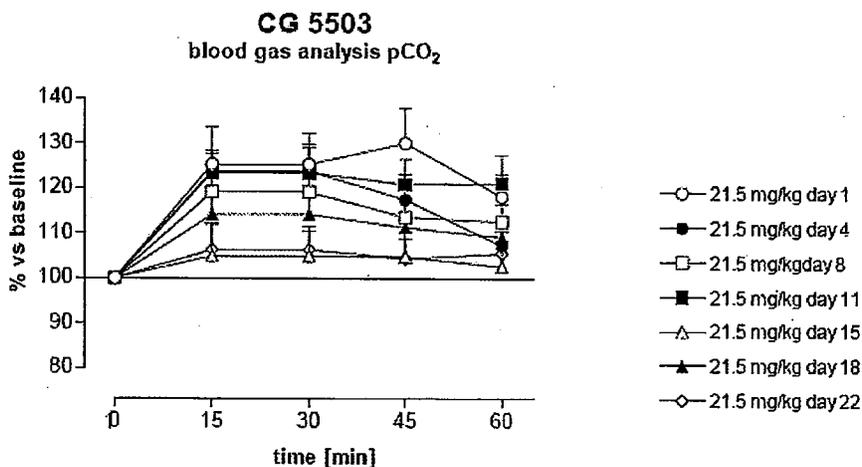
after start of infusion) were observed at the high dose, and decreased femoral blood flow, indicated by increased femoral resistance was found at all doses. The QRS interval was increased (+4%), suggesting decreased rate of ventricular depolarization. There were no treatment-related effects on heart rate, pulmonary arterial pressure, coronary flow and resistance, end-diastolic left ventricular pressure, blood gas measures, and the PR (-10%) and QT intervals, including corrected QT interval (Van de Water's) at the doses tested. Sinoatrial node depression and junctional rhythm development were suggested by decreased (in 3/6 dogs) or eliminated (in 1/6 dogs) P wave amplitude after the 15-minute infusion at the mid-dose and high dose. T wave changes at these doses also suggested treatment-related ventricular repolarization effects, involving either negative inotropic effect or electrophysiological effects on ion channel conductance. The peak serum concentrations studied were 119, 409, and 1177 ng/ml in the males and 151, 561, and 1717 ng/ml in the females at the doses of 0.5, 1.5, and 4.5 mg/kg IV. Although serum concentrations were higher in the female than in the male dogs, there were no statistically significant gender differences in the treatment-related cardiovascular effects by tapentadol.

Pulmonary effects: Respiratory safety pharmacology studies were conducted in Wistar and Sprague Dawley rats administered tapentadol by single and repeated IV and IP injections, and in New Zealand White rabbits by the IV route. The results showed pulmonary effects typically observed following treatment with mu-opioid receptor agonist agents. Tapentadol (referred to as CG5503 in this study) at single IV doses of 4.64 to 14.68 mg/kg decreased spontaneous respiratory frequency in conscious male Wistar rats by up to -38% immediately after HD injection (Study PH389, ED50 0.71 mg/kg vs. 0.23 mg/kg IV for morphine and 10 mg/kg for tramadol HCl). There was a slight dose-dependent inhibition of CO<sub>2</sub>-induced respiratory stimulation in that study. Plethysmography in unrestrained male Wistar rats (Study SP140) given single IV tapentadol doses of 0 (vehicle), and 2-18 mg/kg, produced delayed respiratory stimulation with increased respiratory rate for up to 30 minutes after dosing at 2 mg/kg, and increased minute volume at 2 and 6 mg/kg, suggesting a respiratory stimulant effect at lower doses, and rapid-onset, decreased respiratory rate, peak inspiratory and expiratory flows and minute volume with increased inspiration and expiration times indicating a depressant effect at the high dose of 18 mg/kg IV. There were no treatment-related effects on airway resistance in that study.

In a study on blood gasses (Study SP151), single IV tapentadol injections in male Sprague Dawley rats at 0 (vehicle) and 4.64-14.7 mg/kg resulted in increased arterial blood pCO<sub>2</sub> and decreased pO<sub>2</sub> at doses of ≥ 10 mg/kg. The ED25 in that study, indicating an increase in pCO<sub>2</sub> by 25% compared to baseline was 14.4 mg/kg for tapentadol, vs. 7.9 mg/kg for morphine.

The results of repeated IP injection at 0 (vehicle) and 21.5 mg/kg/day in male Sprague Dawley rats (Study SP177) demonstrated some tolerance to the respiratory depressant effect of tapentadol. In that study, there was an increase in arterial pCO<sub>2</sub> (+43%) indicating respiratory depression on Day 1, with decreasing magnitude of the effect from Dosing 8 onward. Complete tolerance to the respiratory depressant effects was observed

by Dosing Day 22. The rate of tolerance development to the respiratory depression effects was similar to the observed rate of tolerance development to the analgesic effects of tapentadol in the tail flick test in rats in another study (Study PH526), beginning between Days 7-10 of dosing, becoming progressively reduced during Days 18-21, with complete abolishment by Dosing Day 51. The development of tolerance to tapentadol respiratory depressant effects are illustrated in the following figure (provided from the original NDA submission):



**Figure 1:** Changes in arterial pCO<sub>2</sub> following administration of CG5503 at a dose of 21.5 mg/kg i.p. in conscious rats. CG5503 was administered daily for 22 days. Blood gas analysis was performed at days 1, 4, 8, 11, 15, 18 and 22. Data as means  $\pm$  SEM of n = 12 - 13

Correlations of plasma tapentadol and tapentadol O-glucuronide levels, to the time-course of tapentadol-induced respiratory depression, convulsions and deaths were tested in a repeated dose study in male Wistar rats given daily IV tapentadol injections at the dose of 15 mg/kg/day (Study SP142A). Plasma and CSF were sampled at 15-20 minutes and at 12 hours after dosing for parent drug, O-glucuronide metabolite, and sulfate metabolite concentrations, and therefore the absolute T<sub>max</sub> could not be determined. The results showed treatment-related respiratory depression starting 15-20 minutes after infusion, with cyanosis and convulsions in 3/13 rats and deaths in 4/14 rats. There were also late peaks in the incidences of convulsions with cyanosis and deaths at  $\geq$ 12 hours after dosing, and after parent drug and glucuronide metabolite were nearly completely cleared (below level of detection). The peak tapentadol concentrations at the 15-20 minute sampling time-points were around 1000 ng/ml in plasma and CSF, and the peak tapentadol glucuronide metabolite concentration was similar in plasma but approximately 20 ng/ml in CSF. The sulfate metabolite concentration was below the detection limit of 4.9 ng/ml. The late convulsions, cyanosis and deaths observed in the absence of measurable plasma and CSF drug and metabolite concentrations at  $>$ 12 hours after dosing, could not be attributed to plasma and CSF parent or glucuronide and sulfate metabolite concentrations. The Sponsor suggested that potential products of parent drug

or metabolite enrichment in deeper CNS compartments, not detected in plasma and CSF, may have produced these effects, and this issue was not further addressed in the submission. The findings in this study are noted, but not of great concern at this time because there were no clear or repeatable findings of delayed onset or continued findings of neurobehavioral toxicity after drug and metabolite clearance from plasma in the toxicology studies. Whole body autoradiography after single IV (10 mg/kg) tapentadol in rat (Study PK432) showed blood/brain barrier crossing of radioactivity, with brain levels decreasing from peaks of 9.40 and 6.97 mcg equiv/g in brain and spinal cord at 0.25 h, to 4 mcg equiv/g in the CNS at 1 h, 1 mcg equiv/g at 2 h, 0.13 mcg equiv at 4 h, and below detection levels at 8 hours, and therefore a potential metabolic product that may possibly be associated with the delayed neurotoxic signs observed in this study according to speculation by the Sponsor is likely to be cleared rather rapidly. Also, the results of the microscopic examinations in brain in the toxicology studies including the special histopathology evaluation of potential NMDA receptor target site neurotoxicity found no histopathologic evidence of neurotoxicity. Finally, there were no findings in the clinical studies of convulsions or results indicating a potential for delayed or extended adverse CNS and respiratory effects by tapentadol after clearance of the drug in humans.

A study on tapentadol cardiohemodynamic and respiratory effects (referred to as BN200, Study PH323) was conducted in anesthetized New Zealand White rabbits given IV bolus injections at doses from 1-10 mg/kg (in saline solution, up to 3 times the ED50 for efficacy in tooth pulp analgesia in rabbits). The measures were recorded for 1 hour after injection. Respiratory frequencies were reduced 59% and 64% within one minute of injection at 4.64 and 10 mg/kg IV, respectively, and remained reduced by 20% to 40% for the duration of the one-hour observation period. One death in a high dose rabbit (10 mg/kg IV) 5 minutes after dosing was attributed to respiratory depression.

Gastrointestinal effects: Inhibition of intestinal fluid transport and motility are known secondary effects of mu-opioid receptor agonist agents. Potential gastrointestinal effects by tapentadol (referred to as CG5503 in these studies) were tested *in vivo* in ferrets and mice, and in isolated guinea pig ileum. In an emesis model in ferrets (Study PH403A), tapentadol was weakly emetic, inducing retching in 20% of the animals at 14.7 mg/kg IP, and in 40% of the animals at higher doses. Complete emesis was observed in 20% of the ferrets at 10 and 31.6 mg/kg IP.

Tapentadol inhibited gut motility in mice. Charcoal transit distance (Study PH391) was dose-dependently decreased up to a maximum of -48.4% (ED25 = 28 mg/kg IP). In comparison, morphine decreased gut motility in this assay by up to a maximum of -76.8% (ED20 = 5.91 mg/kg IP) and tramadol inhibited charcoal transport up to -50% at 121 mg/kg (ED25 = 66.7 mg/kg IP). In another study (Study PH388), tapentadol inhibited prostaglandin-induced diarrhea in mice (ED50 = 10.3 mg/kg IP), with less potency than morphine (ED50 = 1.12 mg/kg IP). Tapentadol was more potent than tramadol HCl (EC50 = 27.1 mg/kg IP), however, in anti-diarrheal activity.

Tapentadol also inhibited acetylcholine-induced isotonic contractions in isolated guinea pig ileum (Study PH390) *in vitro*, at concentrations of 0.1-2.15 mM, while morphine

had no effect on the isotonic contractions at up to 100 mcM. Atropine was 30 times more potent than tapentadol in this assay (0.001 – 0.01 mcM).

Renal Effects: Renal safety pharmacology parameters were evaluated in four sequential 1-hour periods in conscious male Wistar rats administered tapentadol (referred to as CG5503 in this study) at IV doses of 0 (physiological saline vehicle), 1 and 10 mg/kg (Study PH387). There was no treatment-related effect on urine volume at these doses, and no effects on sodium, potassium and chloride excretion at 1 mg/kg IV in rats. However, at the 10 mg/kg IV dose, electrolyte excretion (sodium, potassium, chloride) was transiently reduced for a duration of one hour.

Other Organ Systems: Potential tapentadol effects on the cholinergic system, particularly on acetylcholine-induced (ACh) effects on smooth and skeletal muscles, were evaluated in PW Guinea Pigs *in vitro*, at concentrations of 0.1-2.15 mcM (Study PH390). Dose-dependent isotonic contractions, induced by ACh in isolated ileal preparations, were inhibited in a concentration-related manner by tapentadol, indicated by a right shift of the concentration-response curve for ACh at all doses tested. The pA<sub>2</sub> value for tapentadol was 6.2, 300 times weaker than that for atropine (pA<sub>2</sub> = 9.7). In comparison, morphine had no effect on ACh-induced contractions in the isolated guinea pig ileum preparations.

In a traction test study on muscle relaxant activity (Study SP166), male NMRI mice received single, bolus IV tapentadol injections at 0 (vehicle), and 4.64-31.6 mg/kg. Tapentadol and the O-glucuronide metabolite had no effects on extent and incidence of muscle relaxation in this study. There were also no interactive effects between tapentadol and diazepam or tetrazepam muscle relaxation scores.

Safety Pharmacology studies on the Metabolites of Tapentadol: Several nonclinical experiments were conducted to assess potential adverse effects by metabolites of tapentadol. The results of a hERG channel assay found lower activity by the O-glucuronide (IC<sub>50</sub> > 120,000 mcg/L), N-methyl (IC<sub>50</sub> = 55,000 mcg/L) and sulfate (IC<sub>50</sub> > 90,000 mcg/L) metabolites than by the parent drug, tapentadol (Study SP131). There were no effects by tapentadol-O-glucuronide on the action potential duration in an *ex vivo* preparation in guinea pig papillary muscles at concentrations of up to 300 mcM (Study SP144).

Abuse liability: Refer to the review by Controlled Substances Division for a detailed assessment of tapentadol abuse liability. Tapentadol abuse liability was evaluated in studies on self-administration in monkeys and induction of physical dependence in mice. Tapentadol maintained self-administration in morphine-experienced rhesus monkeys at doses of 0.01-0.3 mg/kg IV. In mice given multiple doses of tapentadol from 2.15 to 46.4 mg/kg IP over 2 days, and then naloxone (30 mg/kg IP) 2 hours after the last dose, withdrawal jumping was observed at the highest dose in 10% of the mice. In comparison, morphine and tramadol produced naloxone-induced withdrawal jumping at 1.0-4.64 mg/kg IP and 4.64-31.6 mg/kg IP, respectively.

### 3.2.5 Pharmacodynamic drug interactions

Tapentadol potentiated the barbiturate hexobarbital sleep induction time in a study in mice (Study PH385), suggesting interactive CNS depressant effects. There were no drug-drug interactions with diazepam and tetrazepam on muscle relaxation in a traction test in the mouse (Study SP166).

### 3.3 PHARMACOKINETICS/TOXICOKINETICS

The following pharmacokinetic studies on tapentadol were conducted in animals (table provided from the original NDA submission):

Study Description	Species	Route	Manufacturer	Study ID	Notes
Adsorption					
Comparative single dose pharmacokinetics	Mice	Oral, intravenous	Grünenthal, D	PK689	
Single- and repeat dose pharmacokinetics	Rats	Oral (gavage)		PK486/A	
Single- and repeat dose pharmacokinetics	Rats	Intravenous		PK485/A	b(4)
Dose proportionality pharmacokinetics	Rats	Intravenous	Grünenthal, D	PK653	
		Subcutaneous, intraperitoneal			
Single- and repeat dose pharmacokinetics	Rats, mice		Grünenthal, D	TP2232/A	
Single- and repeat dose pharmacokinetics	Dogs	Intravenous		PK483/A	
In vitro absorption	Caco-2, HCT-8	In vitro	Grünenthal, D	PK744	
Distribution					
Protein binding in serum or plasma including melanin binding	Mice, rats, rabbits, dogs, man	In vitro	Grünenthal, D	PK582	b(4)
Single Dose - Tissue distribution of <sup>14</sup> C-tapentadol	Rats	Oral (gavage)		PK432	
Repeat dose - Brain penetration	Rats	Oral (gavage)	Grünenthal, D	PK664	
Metabolism					
	Hamsters, minipigs, dogs, rabbits, rats, mice, Cynomolgus monkey, guinea pigs, human	In vitro	Grünenthal, D	PKN233/A	
Metabolism - in vitro	Mice, rats, dogs, human	In vitro	Grünenthal, D	PK581K/A	
Metabolism - in vivo	Human and rat liver microsomes	In vitro		PK528	b(4)
In vitro glucuronidation	Human hepatoma cells <sup>a</sup> Recombinant human and rat liver enzymes <sup>b</sup>				
Enzyme induction in a toxicological study	Rats	Oral (gavage)		TP2593	
Enzyme induction in a toxicological study	Dogs	Oral (gavage)	Grünenthal, D	TP2415 (PKN268)	
Enzyme induction in a toxicological study	Dogs	Oral (gavage)	Grünenthal, D	TP2441 (PKN309)	
Enzyme induction-inhibition in a toxicological study	Dogs	Intravenous	Grünenthal, D	TP1968/A (PKN118)	
Excretion					
Single-dose - Mass balance ( <sup>14</sup> C-tapentadol)	Mice	Oral (gavage)	Grünenthal, D	PK586/A	
Single-dose - Mass balance ( <sup>14</sup> C-tapentadol)	Rats	Oral (gavage)	Grünenthal, D	PK585	
Single-dose - Mass balance ( <sup>14</sup> C-tapentadol)	Dogs	Oral (gavage)	Grünenthal, D	PK480/A	
Pharmacokinetic Drug Interactions					
Evaluation of induction potential	CYP1A2, 2C9 and 3A4	In vitro		PK679	Located in Module 5
Evaluation of the inhibitory potential	CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A4	In vitro		PK680	Located in Module 5
Co-medication and inhibition of glucuronidation	Human liver microsomes rUGT <sub>1</sub>	In vitro	Grünenthal, D	PK681	Located in Module 5

a) MzHepl and KYN2

b) human: UGT1A6, UGT2B11 and UGT2B4; rat: UGT2B1

The results of the pharmacokinetic studies and toxicokinetic analyses in the toxicology studies indicated rapid oral absorption, but low bioavailability across species. Tapentadol

crosses the blood-brain barrier and placenta, and is weakly protein bound, primarily to albumin in plasma. Tapentadol undergoes first-pass metabolism after oral administration, by N-demethylation and hydroxylation of the aromatic ring in Phase I biotransformation, with Phase II transformation by glucuronidation and sulfate formation. The main circulating metabolite is tapentadol O-glucuronide, which is found at much higher concentrations in plasma than the parent drug in the animal species tested and in humans. Elimination is primarily via renal excretion of the O-glucuronide metabolite. The metabolic profile of tapentadol was found to be similar in rat, dog and human liver microsomes. No active metabolites were detected. The half-life of tapentadol is approximately 0.5-1 hour across doses and across species by IV administration, and approximately 4 hours after IV administration in humans and oral administration in animals and humans. Exposure was generally similar after acute and repeated dose administration, indicating a low potential for accumulation, although increased exposure was found in some of the longer duration studies in the animal species. No effects on hepatic microsomal cytochrome P450 content, 7-ethoxy O-deethylase activity, 2-aminophenol glucuronyltransferase activity, and 4-aminopyrine N-demethylase activity were found in the animal studies, and there was no inhibition of cytochrome P450 by tapentadol in an *in vitro* assay. Therefore the potential for pharmacokinetic drug-drug interactions is low.

### 3.3.3 Absorption

Tapentadol HCl absorption was evaluated *in vitro* and *in vivo* after single and repeat dose administration in mice, rats, rabbits, dog, and monkeys. The *in vitro* model of the intestinal absorption barrier, CACO-2 cell monolayers, was used to examine tapentadol transport in the apical to basolateral direction (Study PK744), at a concentration of 39 mM (8.6 mcg/ml). Unimpeded absorption from the intestine was suggested by a transport rate of  $7.4 \times 10^{-6} \pm 9.4 \times 10^{-7}$ . The results of a study reported in the published literature showed no tendency by tapentadol to inhibit or act as substrate of P-glycoprotein in HCT-8 cells at a concentration of 39 mcM (Hunter et al. 1991); the apical-to-basolateral and basolateral-to-apical transport rates for Rhodamin 123 were unchanged by tapentadol.

The results of a study on single dose absorption in fed and fasted NMRI mice, given IV (8 mg/kg, in sterile physiological saline) and oral (80 mg/kg, in tap water) tapentadol (Study PK689) are presented in the following table (provided from the original NDA submission):

Gender (M/F) / Number of animals	15M	15M	15M	15M
Feeding condition	fed	fed	fasted	fasted
Vehicle/Formulation	Sterile physiological saline / Solution	Sterile physiological saline / Solution	Tap water	Tap water
Method of Administration	intravenous	intravenous	oral	oral
Dose (mg/kg)	8	8	80	80
Sample (whole blood, plasma, serum etc.)	Plasma	Plasma	Plasma	Plasma
Analyte	Tapentadol	Tapentadol O-glucuronide	Tapentadol	Tapentadol O-glucuronide

PK parameters (mean ± Stand Dev)				
AUC <sub>0-∞</sub> (ng·h/mL)	518 ± 59	3690 ± 591	2080 ± 124	43596 ± 6004
AUC <sub>0-1.75h</sub> (ng·h/mL)	513 ± 59	3271 ± 574	1859 ± 62	33949 ± 7509
AUC <sub>0-1.75h</sub> (ng·h/mL) <sup>a</sup>	64.1 ± 7.4	409 ± 71.8	23.2 ± 0.78	424 ± 93.9
C <sub>max</sub> (ng/mL)	1427 ± 148	3358 ± 1085	5785 ± 2067	32128 ± 8464
C <sub>max</sub> (ng/mL) <sup>a</sup>	178 ± 18.5	420 ± 136	72.3 ± 25.8	402 ± 106
t <sub>max</sub> (h)	0.08 ± 0.0	0.31 ± 0.19	0.08 ± 0.0	0.42 ± 0.0
t <sub>1/2</sub> (h)	0.29 ± 0.04	0.51 ± 0.11	0.64 ± 0.01	0.78 ± 0.24
CL/f (mL/min/kg)	223 ± 27	n.c.	552 ± 34	n.c.
Vz (L/kg)	5.6 ± 1.4	n.c.	30.7 ± 2.2	n.c.
F [%]	--	--	40.3 ± 2.6	--

a) dose normalized to 1 mg/kg

Oral absorption was rapid in mice, with peak plasma levels (C<sub>max</sub>) observed at 0.08 hour after the single dose by either route, although the half life was longer following oral (0.64 h) than IV (0.29 h) administration. Oral tapentadol bioavailability was approximately 40%.

Repeated IP (10, 25, and 50 mg/kg/day, in physiological saline) and SC (25, 50, and 100 mg/kg/day, 100 mg/kg/day dose reduced to 10 mg/kg/day due to severe clinical signs, in physiological saline) administration in NMRI mice for 14 days (Study TP2232) revealed higher exposure by the SC than by the IV route. The half life values were similar by both routes, at approximately 0.5 hour. There was no evidence of accumulation in the exposure levels after 2 weeks when compared to exposure after the first dose. The results of the 14-day study in NMRI mice are presented below (table provided from the original NDA submission):

Method of Administration Dose (mg/kg) Repeated doses	Intraperitoneal 10		Intraperitoneal 25		Intraperitoneal 50	
	First	Last	First	Last	First	Last
PK parameters (mean ± Stand Dev)						
AUC(ng·h/mL)	n.c. <sup>a</sup>	n.c.	441 ± 255	234 ± 63	1112 ± 338	564 ± 114
AUC <sub>0-4</sub> (ng·h/mL)	155 ± 46	128 ± 53	387 ± 194	236 ± 55	1108 ± 338	457 ± 281
C <sub>max</sub> (ng/mL)	229.9 ± 64.9	150.9 ± 35.9	577.3 ± 347.7	317.1 ± 91.2	1711 ± 616	592.3 ± 358
t <sub>max</sub> (min)	0.5 ± 0	0.5 ± 0	0.5 ± 0	0.5 ± 0	0.5 ± 0	0.8 ± 0.67
t <sub>1/2</sub> (min)	n.c. <sup>a</sup>	n.c. <sup>a</sup>	0.49 ± 0.10	0.54 ± 0.10	0.43 ± 0.05	0.44 ± 0.03
CL/f (mL/min/kg)	n.c. <sup>a</sup>	n.c. <sup>a</sup>	1099 ± 784	1984 ± 720	685 ± 175	1294 ± 261

Method of Administration Dose (mg/kg) Repeated doses	subcutaneous 25		subcutaneous 50		subcutaneous 100	
	First	Last	First	Last	First	Last
PK parameters (mean ± Stand Dev)						
AUC(ng·h/mL)	595 ± 341	827 ± 88	1908 ± 90	1810 ± 259	4805 ± 121	-
AUC <sub>0-4</sub> (ng·h/mL)	592 ± 341	808 ± 93	1774 ± 104	1807 ± 258	5010 ± 498	-
C <sub>max</sub> (ng/mL)	826.8 ± 567.5	1128.5 ± 98.4	2747 ± 143	2740.8 ± 397.9	6999.7 ± 312.6	-
T <sub>max</sub> (min)	0.5 ± 0	0.5 ± 0	0.5 ± 0	0.5 ± 0	0.5 ± 0	-
T <sub>1/2</sub> (min)	0.46 ± 0.08	0.56 ± 0.21	0.39 ± 0.03	0.38 ± 0.02	0.42 ± 0.04	-
CL/f (mL/min/kg)	826 ± 515	436 ± 44	397 ± 19	401 ± 49	298 ± 8	-

a) not calculated

Additional information on repeated dose tapentadol pharmacokinetics (PK) in mice was provided by the toxicokinetic (TK) analyses performed in the toxicology studies. Oral tapentadol systemic exposure was found to be higher when administered by gavage than by the dietary route, in a 14-day study (Study TP2470). In that study, CD-1 mice were given gavage doses ranging from 50-250 mg/kg/day, and dietary doses from 50-200 mg/kg/day. The results showed approximately 33 times higher C<sub>max</sub> and 3.5 times

higher AUC values using gavage methodology. Exploration of potential treatment-duration effects found mixed results, with decreased exposure, particularly at higher dose levels in one 13-week study in CD-1 mice (Study TP2496), but no differences in exposure over the duration of treatment in another 13-week study (Study TP2379) and in the 2-year carcinogenicity study (Study2518) in NMRI mice. There were no gender differences in systemic drug exposure in the PK and TK assessments in most studies in mice.

Characterization of tapentadol pharmacokinetic (PK) parameters in rat was conducted in specific PK studies and in the toxicokinetic (TK) analyses in the toxicology studies. Absorption by the oral route was found to be rapid (T<sub>max</sub> 0.25 hour), but incomplete, with bioavailability of approximately 9% in a single dose study in male Wistar rats given intravenous (IV) and oral (PO) tapentadol (Studies PK485/A and PK486/A). The results of that study are presented in the following table:

**Pharmacokinetic Parameters in male Wistar rats (n=10) after Single IV and Oral Tapentadol Administration (means ± SD)**

Parameter	7 mg/kg IV Tapentadol	300 mg/kg PO Tapentadol
AUC (ng.h/ml)	442 ± 36	1711 ± 478 (0-12h)
C <sub>max</sub> (ng/ml)	792 ± 82	866 ± 542
T <sub>max</sub> (h)	Reference (0.0)	0.25 (range 0.25-1)
T <sub>1/2</sub> (h)	0.53 ± 0.05	Not calculated
CL (ml/min/kg)	228 ± 19	Not calculated
V <sub>d</sub> (l/kg)	10.4 ± 1.3	Not calculated
MRT (h)	0.60 ± 0.046	Not calculated
F (%)	Reference (100%)	9

The apparent low bioavailability of the parent drug by the oral route in rats is probably due to rapid first-pass metabolism; urinary excretion measurements on radiolabeled tapentadol and metabolites (Study PK586/A) demonstrated total absorption of ≥70% in male and ≥94% in female Wistar rats.

Systemic tapentadol (referred to as CG5503 in that study) exposure (AUC) was found to be dose-proportional in rat using IV doses of 3.5, 7, and 14 mg/kg (Study PK653), with no evidence of gender differences in exposure. The results are presented in the following table (provided from the original NDA submission):

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Pharmacokinetic parameters of CG5503 base after single intravenous administration of different doses to female rats (n = 4 per group; mean ± SD):

Parameters		Doses		
		3.5 mg/kg	7.0 mg/kg	14 mg/kg
AUC <sub>0-∞</sub>	[ng · h /mL]	166 ± 56	639 ± 346	1051 ± 99
AUC <sub>0-t</sub>	[ng · h /mL]	165 ± 57	627 ± 328	1049 ± 98
C <sub>max</sub>	[ng/mL]	299 ± 82	830 ± 100	1739 ± 146
t <sub>1/2,z</sub>	[h]	0.70 ± 0.08	1.98 ± 1.14	2.05 ± 1.03
MRT	[h]	0.68 ± 0.03	1.17 ± 0.64	0.84 ± 0.14
CL	[mL/min/kg]	328 ± 108	190 ± 86	192 ± 17
V <sub>z</sub>	[L /kg]	19.8 ± 6.6	35.6 ± 35.0	34.9 ± 18.0

There were also no changes in systemic exposure in Wistar rats over a period of 7 days in a study that examined PK parameters of IV tapentadol given twice daily at 7 mg/kg/day b.i.d. (Study PK485/A), and therefore no evidence of accumulation with IV dosing in the short term in rat. The results of the 7-day investigation of potential repeated dose effects on exposure in rats are presented in the following table (provided from the original NDA submission), for the first and second dose on Day 1 and the last dose on Day 7:

Summary Table: Pharmacokinetic parameters

parameter	unit	i.v. single dose		i.v. multiple dose, day 1		i.v. multiple dose, day 7	
		Mean	± SD	Mean	± SD	Mean	± SD
AUC <sub>0-∞</sub> (Dose normal.)	ng.h/ml	73.54	± 5.98	74.75	± 7.52	73.96	± 11.33
β	1/min	0.0221	± 0.0020	0.0198	± 0.0040	0.0212	± 0.0047
t <sub>1/2</sub>	min	31.82	± 2.79	36.61	± 9.11	34.59	± 10.10
Cl	ml/min/kg	228.0	± 19.3	225.0	± 22.4	229.6	± 33.1
Vd <sub>area</sub>	L/kg	10.40	± 1.26	11.92	± 3.32	11.22	± 2.43
MRT	min	35.85	± 2.78	37.93	± 5.36	39.83	± 4.72
Accumulation ratio						0.9895 <sup>a</sup>	

<sup>a</sup> Calculated as: mean AUC<sub>0-12h</sub> (day 7) / mean AUC<sub>0-12h</sub> (day 1)

Comparison of PK parameters by IP (10, 25 and 50 mg/kg/day for 14 days) vs, SC (25, 50, and 100 mg/kg/day) routes in Sprague Dawley rats demonstrated 3-4 times higher systemic exposure by the SC route (Study TP2232), but no differences in exposure with increased duration of treatment (no accumulation) and no differences in terminal half-life of 0.6-1h after the first and last doses.

Repeated dose oral PK parameters in rats were characterized from TK measurements in the subchronic and chronic toxicology studies. Unlike the findings in most of the nonclinical toxicology studies, increased systemic exposure (up to 4X) was found over a period of 3 months in rats administered tapentadol by oral gavage twice daily at doses of 30, 100, and 200 mg/kg/day, 5 hours apart (Study TP2645), and by once daily oral gavage administration study of 26 weeks duration at doses of 75, 150, and 300 mg/kg/day (Study TP2397). The results of the exposure data from the 13- and 26-week oral gavage

toxicology studies are presented in the following tables (provided from the original NDA submission):

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 $\pm$ 79	1 031 $\pm$ 282	4 042 $\pm$ 772	289 $\pm$ 250	1 307 $\pm$ 315	4 854 $\pm$ 548
$C_{max}$	[ng/ml]	91 $\pm$ 58	301 $\pm$ 237	1 281 $\pm$ 726	156 $\pm$ 136	479 $\pm$ 55	1 094 $\pm$ 910
Week 13							
AUC	[ng·h/ml]	1 034 $\pm$ 528	2 254 $\pm$ 106	4 828 $\pm$ 1 559	979 $\pm$ 382	4 222 $\pm$ 226	11 829 $\pm$ 2 649
$C_{max}$	[ng/ml]	414 $\pm$ 225	758 $\pm$ 580	1 244 $\pm$ 447	425 $\pm$ 232	1 409 $\pm$ 145	3 733 $\pm$ 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

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†
On day 1									
$C_{max}$	[ $\mu$ g/L] $\pm$ Stand Dev	65 $\pm$ 55	250 $\pm$ 155	623 $\pm$ 447	453 $\pm$ 350	45 $\pm$ 9	167 $\pm$ 59	166 $\pm$ 34	789 $\pm$ 322
$AUC_{0-24}$	[ $\mu$ g·h/L] $\pm$ Stand Dev	77 $\pm$ 19	255 $\pm$ 91	445 $\pm$ 161	679 $\pm$ 291	79 $\pm$ 13	249 $\pm$ 41	302 $\pm$ 53	1067 $\pm$ 520
Week 4									
$C_{max}$	[ $\mu$ g/L] $\pm$ Stand Dev	117 $\pm$ 32	311 $\pm$ 374	961 $\pm$ 1308	411 $\pm$ 132	237 $\pm$ 24	295 $\pm$ 56	507 $\pm$ 118	2934 $\pm$ 1632
$AUC_{0-24}$	[ $\mu$ g·h/L] $\pm$ Stand Dev	176 $\pm$ 52	233 $\pm$ 147	434 $\pm$ 408	541 $\pm$ 182	407 $\pm$ 71	398 $\pm$ 75	1075 $\pm$ 201	1986 $\pm$ 660
Week 13									
$C_{max}$	[ $\mu$ g/L] $\pm$ Stand Dev	314 $\pm$ 18	429 $\pm$ 59	1312 $\pm$ 398	1250 $\pm$ 1216	538 $\pm$ 492	656 $\pm$ 204	695 $\pm$ 128	848 $\pm$ 302
$AUC_{0-24}$	[ $\mu$ g·h/L] $\pm$ Stand Dev	396 $\pm$ 223	375 $\pm$ 26	874 $\pm$ 150	1236 $\pm$ 764	542 $\pm$ 295	844 $\pm$ 370	1032 $\pm$ 268	1530 $\pm$ 660
Week 26									
$C_{max}$	[ $\mu$ g/L] $\pm$ Stand Dev	252 $\pm$ 113	507 $\pm$ 173	1451 $\pm$ 8	nd	520 $\pm$ 422	451 $\pm$ 129	912 $\pm$ 1072	nd
$AUC_{0-24}$	[ $\mu$ g·h/L] $\pm$ Stand Dev	391 $\pm$ 229	1060 $\pm$ 366	1987 $\pm$ 779	nd	857 $\pm$ 480	1461 $\pm$ 432	3088 $\pm$ 1482	nd

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

nd = No data.

No changes in systemic exposure over the dosing period were observed in male and female Wistar rats after subchronic (13-week) treatment (Study TP2380) at doses of 250-1000 mg/kg/day by dietary admixture, nor after chronic (26-week) tapentadol treatment by dietary admixture at doses of 10-250 mg/kg/day in the 2-year carcinogenicity study (Study TP2418). There was high variability in exposure in those studies, however, that was possibly due to interference with feeding in some rats in the grouped-caging arrangement. However, it was evident that there was increased exposure with dose, and exposure appeared to be 2-3 times higher in the female than in the male rats. The results of exposure calculations in those studies are presented in the following tables (provided from the original NDA submission):

The mean exposure of CG5503 base and CG5503 glucuronide is listed in the following table:

Target dose [mg/kg/day]	Time	AUC <sub>0-24h</sub> CG5503 base [ng/mL]		AUC <sub>0-24h</sub> CG5503 glucuronide [ng/mL]	
		Male	Female	Male	Female
250	Day 3	742	772	296606	394590
	Week 6	737	737	317478	379329
	Week 13	470	1323	275270	395755
	all weeks	650 ± 156	944 ± 329	296451 ± 21104	389891 ± 9166
500	Day 3	891	1476	679791	708379
	Week 6	906	3118	566246	814598
	Week 13	700	2462	641050	694388
	all weeks	832 ± 115	2352 ± 826	629029 ± 57719	739122 ± 65738
1000	Day 3	1736	2345	n.d.	n.d.
	Week 6	2095	3369	n.d.	n.d.
	Week 13	1841	1404	n.d.	n.d.
	all weeks	1891 ± 184	2373 ± 983	--	--

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Summary on exposure to CG5503 glucuronide in Wistar rats after daily oral doses of CG5503 in the diet for at least 104 weeks  
(mean values C<sub>max</sub> and AUC<sub>(0-24h)</sub> ± S.D. of week 4, week 13 and week 26)

Dose	[mg/kg/day]	Males				Females			
		10	50	125	250	10	50	125	250
Week 4									
AUC	[ng·h/ml]	18630 ±4778	88881 ±22176	221058 ±49522	428530 ±167827	15750 ±4419	80647 ±20367	213118 ±8960	396595 ±181995
Week 13									
AUC	[ng·h/ml]	21977 ±1877	94668 ±20658	249068 ±66631	462639 ±98040	19312 ±6475	104501 ±24954	263560 ±51050	495182 ±158659
Week 26									
AUC	[ng·h/ml]	19534 ±6919	102417 ±29299	277884 ±111166	475181 ±181040	16881 ±4422	98980 ±32854	285241 ±95222	436231 ±150146
Weeks 4 to 26									
AUC	[ng·h/ml]	20047 ±4563	95322 ±17707	249337 ±71028	455450 ±111894	17315 ±3904	94709 ±18638	253973 ±64122	442669 ±132524
R <sub>A2</sub>	[%]	105	115	126	111	107	123	134	110

R<sub>A2</sub> = ratio of AUC from week 26 to week 4

Tapentadol PK parameters in the rabbit were investigated in the IV and SC studies in pregnant females to evaluate potential adverse effects on embryo-fetal development. These studies showed rapid absorption and dose-linear increases in exposure, with no evidence of accumulation over the 2-week dosing periods. The results of these studies, showing TK parameters by the IV (Study TP2062) route at doses of 1, 3, and 9 mg/kg/day and by the SC (Study TP2511) route at doses of 2, 5, and 12 mg/kg b.i.d., 8 hours apart (4, 10 and 24 mg/kg/day) are presented in the following tables (provided from the original NDA submission):

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**Table 1: Serum concentrations of CG5503-base [ng/ml] after the first intravenous administration to pregnant rabbits**

Daily dose: 1, 3 or 9 mg/kg CG5503

Dose [mg/kg]	Time [h]	Animal no.			Mean	S.D.	S.E.M.	C.V. [%]	N
		24	25	26					
1	0.00	✓			n.c.	n.c.	n.c.	n.c.	0
	0.25				137.9	45.1	26.0	32.7	3
	1.00				53.8	2.4	1.4	4.5	3
	2.00				18.7	6.4	3.7	34.3	3

b(4)

Dose [mg/kg]	Time [h]	Animal no.			Mean	S.D.	S.E.M.	C.V. [%]	N
		42	43	44					
3	0.00	✓			n.c.	n.c.	n.c.	n.c.	0
	0.25				371.0	67.0	38.7	18.1	3
	1.00				174.0	9.8	5.5	5.5	3
	2.00				70.7	12.4	7.1	17.5	3

b(4)

Dose [mg/kg]	Time [h]	Animal no.			Mean	S.D.	S.E.M.	C.V. [%]	N
		62	63	64					
9	0.00	✓			n.c.	n.c.	n.c.	n.c.	0
	0.25				1543.8	291.2	168.1	18.9	3
	1.00				569.0	118.1	68.2	20.8	3
	2.00				197.8	31.5	18.2	15.9	3

b(4)

<#.# : value below limit of quantification

n.c. : not calculated

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**Table 2: Serum concentrations of CG5503-base [ng/ml] after the 15th intravenous administration to pregnant rabbits**

Daily dose: 1, 3 or 9 mg/kg CG5503

Dose [mg/kg]	Time [h]	Animal no.			Mean	S.D.	S.E.M.	C.V. [%]	N
		24	25	26					
1	0.00	✓			n.c.	n.c.	n.c.	n.c.	0
	0.25				120.8	12.4	7.2	10.3	3
	1.00				49.9	10.4	6.0	20.8	3
	2.00				21.8	7.7	4.4	35.3	3

Dose [mg/kg]	Time [h]	Animal no.			Mean	S.D.	S.E.M.	C.V. [%]	N
		42	43	44					
3	0.00	✓			n.c.	n.c.	n.c.	n.c.	0
	0.25				415.1	63.8	36.9	15.4	3
	1.00				143.9	28.6	16.5	19.9	3
	2.00				60.4	13.8	8.0	22.9	3

Dose [mg/kg]	Time [h]	Animal no.			Mean	S.D.	S.E.M.	C.V. [%]	N
		62	63	64					
9	0.00	✓			1.1				1
	0.25				1339.1	212.5	122.7	15.9	3
	1.00				531.3	60.3	34.8	11.3	3
	2.00				217.6	57.5	33.2	26.4	3

<##: value below limit of quantification

n.c.: not calculated

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**Table 3.1:** Mean ( $\pm$  S.D.) pharmacokinetic parameters of CG5503 base after subcutaneous administration of CG5503 to pregnant rabbits (day 6)

		Dose [mg/kg/day]		
		4	10	24
AUC	[h·ng/ml]	299 $\pm$ 78.6	947 $\pm$ 86.3	2505 $\pm$ 443
AUC <sub>0-t</sub>	[h·ng/ml]	297 $\pm$ 76.9	944 $\pm$ 85.8	2492 $\pm$ 430
C <sub>max</sub>	[ng/ml]	131 $\pm$ 12.6	519 $\pm$ 95.5	1221 $\pm$ 96.6
t <sub>max</sub>	[h]	0.50 $\pm$ 0.43	0.25 $\pm$ 0.00	0.75 $\pm$ 0.43
t <sub>1/2,z</sub>	[h]	0.97 $\pm$ 0.09	0.93 $\pm$ 0.05	0.96 $\pm$ 0.14
CL/f	[ml/min/kg]	99.8 $\pm$ 23.7	76.0 $\pm$ 7.26	69.9 $\pm$ 11.4
V <sub>d</sub> /f	[l/kg]	8.27 $\pm$ 1.44	6.10 $\pm$ 0.54	5.74 $\pm$ 0.34

**Table 3.2:** Mean ( $\pm$  S.D.) pharmacokinetic parameters of CG5503 base after subcutaneous administration of CG5503 to pregnant rabbits (day 20)

		Dose [mg/kg/day]		
		4	10	24
AUC	[h·ng/ml]	307 $\pm$ 41.4	960 $\pm$ 146	2871 $\pm$ 305
AUC <sub>0-t</sub>	[h·ng/ml]	304 $\pm$ 39.5	955 $\pm$ 145	2835 $\pm$ 286
C <sub>max</sub>	[ng/ml]	149 $\pm$ 20.9	582 $\pm$ 141	1513 $\pm$ 401
t <sub>max</sub>	[h]	0.50 $\pm$ 0.43	0.25 $\pm$ 0.00	0.25 $\pm$ 0.00
t <sub>1/2,z</sub>	[h]	1.13 $\pm$ 0.17	1.01 $\pm$ 0.06	1.18 $\pm$ 0.19
CL/f	[ml/min/kg]	94.4 $\pm$ 13.7	75.8 $\pm$ 12.5	60.3 $\pm$ 6.82
V <sub>d</sub> /f	[l/kg]	9.20 $\pm$ 1.42	6.64 $\pm$ 1.15	6.12 $\pm$ 0.57

Single and repeated dose tapentadol pharmacokinetics (PK) were assessed Beagle dogs, with additional information provided in the TK measurements in the sub-acute, sub-chronic and chronic dose range-finding and toxicology studies. Oral (gavage) absorption was rapid, but oral bioavailability was low (approximately 3%), presumably as a result of extensive first-pass metabolism. No accumulation was found in a comparison of exposure after dosing for 7 consecutive days with exposure after the first dose by the IV route, but exposure appeared higher after 7 days than after the first of 7 daily doses by the oral (PO) route, indicated by higher C<sub>max</sub> and AUC values (Study PK483/A). The results of that study, showing single and 7-day repeated IV (5 mg/kg b.i.d.) and PO (100 mg/kg b.i.d.) dose PK parameters in Beagle dogs are presented in the following table (provided from the original NDA submission):

Species	Dog (Beagle)		Dog (Beagle)	
	4M	4M	4M	4M
Gender (M/F) / Number of animals	4M	4M	4M	4M
Feeding condition	Fed <sup>a</sup>	Fed <sup>a</sup>	Fed <sup>a</sup>	Fed <sup>a</sup>
Vehicle/Formulation	Physiological saline / Solution	Physiological saline / Solution	Milli-U Water / Solution	Milli-U Water / Solution
Method of Administration	Intravenous	Intravenous	Oral	Oral
Dose (mg/kg)	5 bid <sup>b</sup>	5 bid <sup>b</sup>	100 bid <sup>b</sup>	100 bid <sup>b</sup>
Sample (whole blood, plasma, serum etc.)	Plasma	Plasma	Plasma	Plasma
Analyte	Tapentadol	Tapentadol	Tapentadol	Tapentadol
Assay	HPLC <sup>c</sup>	HPLC <sup>c</sup>	HPLC <sup>c</sup>	HPLC <sup>c</sup>
Repeated doses	First	Last	First	Last
PK parameters (mean ± Stand Dev)				
AUC <sub>0-∞</sub> (ng·h/mL)	577.8 ± 250.3	642.8 ± 145.2	180.7 ± 50.2	458.8 ± 414.6
AUC <sub>0-t</sub> (ng·h/mL) <sup>d</sup>	115.6 ± 50.1	128.6 ± 29.0	1.81 ± 0.50	4.59 ± 4.15
AUC <sub>0-1h</sub> (ng·h/mL) <sup>e</sup>	574.9 ± 248.3	638.6 ± 146.1	153.8 ± 37.3	440.7 ± 424.0
C <sub>max</sub> (ng/mL)	692.3 ± 83.2	891.5 ± 199.7	40.8 ± 8.3	346.3 ± 490.5
t <sub>max</sub> (min)	-	-	0.88 (0.75-1.5) <sup>f</sup>	0.38 (0.25-0.5) <sup>f</sup>
t <sub>1/2</sub> (h)	0.88 ± 0.14	1.0 ± 0.16	4.5 ± 2.3 <sup>d</sup>	5.2 ± 1.3 <sup>d</sup>
CL <sub>app</sub> (mL/min/kg)	137.3 ± 41.7	115.8 ± 26.9	-	-
CL <sub>app</sub> /f (mL/min/kg)	-	-	8376 ± 2221	4708 ± 2471
V <sub>z</sub> (L/kg)	10.4 ± 3.7	10.4 ± 2.8	-	-
MRT (h)	0.88 ± 0.09	1.14 ± 0.23	5.71 ± 1.92	4.27 ± 1.44
MAT (h)	-	-	4.82 ± 1.84	3.14 ± 1.26

(Continued)

- a) feeding was finished approximately 2 hours prior to the first dosing
- b) twice daily every 12 hours for 7 days
- c) fluorescence detection
- e) dose normalized to 1mg/kg
- f) one or more approximate values used for calculation of mean
- g) median and range

The results of TK measurements in a 3-month SC dose range-finding study in Beagle dogs given doses of 10, 20, and 40 mg/kg b.i.d. during a dose escalation phase, followed by 20 mg/kg b.i.d. in a treatment phase from Days 14-91 (Study TP2455) showed rapid absorption, with peak plasma concentrations at approximately 0.4-0.5 hours after the second dose and after the 20 mg/kg dose during both the dose escalation and the treatment phases. No evidence of increased exposure with duration of treatment was found, and thus there was no evidence of accumulation over 3 months treatment in the dogs by the SC route at the doses studied. The exposure to the tapentadol O-glucuronide metabolite was approximately 12-14 times higher than exposure to the parent drug, and the half-life was longer for the metabolite (4 hours) as well, compared to the tapentadol half-life (1.8 hour). The TK parameters after the first and second dose of 20 mg/kg on Day 91 are shown below (table provided from the original NDA submission):

Parameters	Pharmacokinetic parameters after s.c. administration of 20 mg/kg bid (40 mg/kg/day) to male Beagle dogs			
	On Day 91 (after the 1 <sup>st</sup> and 2 <sup>nd</sup> dose)		CG5503 glucuronide	
		CG5503 base		
AUC [h · ng/mL]		9 270 ± 570	140 889 ± 22 047	
AUC <sub>0-t</sub> [h · ng/mL]		9 264 ± 571	133 559 ± 14 290	
MRT [h]		5.51 ± 0.56	nd	
C <sub>max</sub> [ng/mL]		1 965 ± 478	11 952 ± 830	
t <sub>max</sub> [h]		nd	10.0 ± 0.0	
t <sub>1/2</sub> [h]		1.77 ± 0.07	4.04 ± 1.28	
CL [mL/min/kg]		61.9 ± 3.7	nd	
V <sub>z</sub> [L/kg]		9.50 ± 0.86	nd	

nd - No data.

Toxicokinetic assessments in a second 13-week SC dose range-finding study Beagle dogs (TP 2559) at doses of 2, 4, and 8 mg/kg b.i.d. demonstrated no differences in exposure to the parent drug as a function of gender or treatment duration, although exposure to the tapentadol O-glucuronide metabolite was somewhat lower in the females than in the males, and tended to decrease with increasing treatment duration from 1 to 13 weeks. The results showed dose-proportional increases in exposure. The results are presented below (table provided from the original NDA submission):

Daily Dose (mg/kg)		0 (Control)		4		8		16	
		6M	6F	4M	4F	4M	4F	6M	6F
<b>Toxicokinetics</b>									
<b>AUC<sub>0-9</sub> (ng·h/mL)</b>									
Tapentadol base	day 1	0	0	204.0	216.5	413.1	487.4	796.5	681.1
	week 13	0	0	239.3	227.9	529.2	526.9	1047	909.3
Tapentadol O-glucuronide	day 1	0	0	2753	2807	7847	5553	13616	13383
	week 13	0	0	2827	2459	6912	5191	12133	12697
<b>C<sub>max</sub> (ng/mL)</b>									
Tapentadol base	day 1	0	0	141.2	133.0	353.5	325.8	712.8	541.3
	week 13	0	0	149.2	110.4	339.1	335.7	619.6	625.4
Tapentadol O-glucuronide	day 1	0	0	954	966	3299	1975	5596	5361
	week 13	0	0	843	696	2041	1522	3327	3887

Repeated oral (gavage) dose tapentadol TK parameters were evaluated in Beagle dogs given doses of 10, 35, and 120 (reduced to 80 on Day 22) mg/kg/day (Study TP2415). The results showed greater than dose-proportional increases in exposure to the parent drug, with higher exposure in the males than in the females except at the mid-dose. There was little evidence of accumulation over 3 months. The results of the TK evaluation in that study are presented in the following table (provided from the original NDA submission):

Dose CG5503 [mg/kg]	Time [h]	C <sub>max</sub> ± S.D. [ng/ml]	C <sub>max</sub> ± S.D. [ng/ml]	AUC <sub>0-t</sub> ± S.D. [h·ng/ml]	AUC <sub>0-t</sub> ± 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

No meaningful treatment duration-related changes in exposure were observed in the 13-week oral gavage study described above, and at comparable oral gavage doses (10, 30, and 80 mg/kg/day) administered to Beagle dogs for 52 weeks in the pivotal toxicology study (Study TP2441). Hence, there was no evidence of accumulation of parent drug nor of the glucuronide metabolite in chronically treated dogs. There was a greater than dose-proportional increase in exposure, but no differences based on gender. Additionally, there were no changes in the mean terminal half-lives (range 6-9 hours) as a result of chronic administration. The results of the TK analyses in the 52-week study in dogs are presented below (table provided from the original NDA submission):

**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.		$\pm 2102$	$\pm 3870$	$\pm 8201$	$\pm 2433$	$\pm 5772$	$\pm 13836$
$AUC_{0-4}$	[ $\mu\text{g}\cdot\text{h/L}$ ]	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.		$\pm 1808$	$\pm 6650$	$\pm 7380$	$\pm 2433$	$\pm 9415$	$\pm 21362$
$AUC_{0-4}$	[ $\mu\text{g}\cdot\text{h/L}$ ]	32044	88313	224693	24138	84304	231142
S.D.		$\pm 8146$	$\pm 18485$	$\pm 38779$	$\pm 7936$	$\pm 22197$	$\pm 100293$

The TK observations in the 2-week IV (5 mg/kg/day) and oral gavage (15 mg/kg/day) pilot study in Cynomolgus monkeys (Study TP2316, see review, below) showed extremely low systemic exposure to the parent drug, tapentadol by the PO route compared to exposure after IV dosing, probably due to extensive and rapid first-pass metabolism in this species. The oral bioavailability was <1%. The PK values were generally stable over the 14-day duration of treatment, presumably due in part to a short half life, and so accumulation is unlikely. Tapentadol was widely distributed ( $V_d = 5.8$  l/kg) in the monkeys. The half life by oral administration was approximately 1 hour.

Comparative oral tapentadol bioavailability in rat, dog and human (presented in the following table from the Sponsor), as well as findings of higher exposure to the glucuronide metabolite in the nonclinical studies compared to exposure in the human studies suggests more extensive tapentadol metabolism in the animal species tested.

**Bioavailability of CG5503: comparison of rat, dog and human data**

	rat <sup>1</sup>	dog <sup>2</sup>	human
AUC p.o.	1993 $\pm$ 557 h·ng/ml (dose: 300 mg/kg)	320 $\pm$ 270 h·ng/ml (dose: 100 mg/kg)	190 h·ng/ml (dose: 60 mg)
AUC i.v.	514 $\pm$ 42 h·ng/ml (dose: 7 mg/kg)	596 $\pm$ 139 h·ng/ml (dose: 5 mg/kg)	588 h·ng/ml (dose: 60 mg)
F	0.6 %	2.7 %	32.3 %

<sup>1</sup> Data from FE-PK 485 (i.v.) and FE-PK 486 (p.o.)

<sup>2</sup> Crossover data from FE-PK 483

**Study title: Pilot Study on the Toxicokinetics and the Toxicity of CG5503 After Repeated Intravenous and Oral Administrations to Cynomolgus Monkeys**

**Key study findings:**

- No differences in serum drug concentrations on Days 1 and 14 after IV administration suggested no accumulation with repeated dosing
- Oral bioavailability at 15 mg/kg/day extremely low (<1%), suggested poor absorption or high first-pass metabolism
- Short oral half-life of ≈1 hour
- Large Vd (5.8 l/kg)
- Results suggest that extremely high doses would be required to attain adequate exposure to the test article in long-term toxicity studies in monkeys, and therefore this species is likely not an appropriate species for nonclinical toxicologic evaluation to support human safety.

**Study no.:** TP2316

**Conducting laboratory and location:** [ ] [ ] [ ]

b(4)

**Date of study initiation:** April 10, 2000

**GLP compliance:** Yes

**QA report:** yes (x) no ( )

**Drug CG5503 (BN 200, tapentadol), lot # Batch CEHS 93-95/part 2, and % purity:**  
97.4%

**Methods**

**Doses:** 5 mg/kg/day IV and 15 mg/kg/day PO

**Species/strain:** Cynomolgus monkeys (*Macaca fascicularis*)

**Number/sex/group or time point (main study):** 3M/group

**Route, formulation, volume, and infusion rate:** CG5503 was dissolved in 0.9% physiological saline (NaCl), injected intravenously (IV, *vena saphena*) at 1 ml/kg (2 min/dosage); following a 17-Day washout period, CG5503 was administered orally (15 mg/kg/day, 2 ml/kg) by gavage, once daily for 14 consecutive days

**Satellite groups used for toxicokinetics or recovery:** None

**Age:** 46-97 months

**Weight:** 3.5-4.4 kg

**Unique study design or methodology:** The monkeys were housed singly in steel cages in a temperature and humidity controlled animal room, with 12-hour light/dark cycle. The monkeys were provided [ ] diet at 60 g/kg BW *ad libitum* daily, divided into 2 feedings. Tap water was provided *ad libitum*.

b(4)

**Observation times**

**Mortality:** Twice daily.

**Clinical signs:** At least once daily, and immediately after administration, until any observed signs were resolved.

**Body weights:** Baseline, Dosing Day 2, and weekly.

**Food consumption:** Daily throughout the study.

**Injection site:** Examined daily.

**Ophthalmoscopy:** Not done.

**EKG:** Not done.

**Clinical Laboratory Evaluations:** Not done.

**Necropsy/Organ Weights/Histopathology:** Not done.

**Toxicokinetics:** Days 1 and 14, at 0 (before dosing), 30 and 120 minutes after IV injection, and on Day 32 at 0, 30 and 120 minutes and Day 45 at 0, 10, 20, 30, 60, 90, and 240 minutes after oral dosing.

## Results

**Mortality:** There were no deaths during the study.

### **Clinical signs:**

- Slight sedation after IV dosing on Days 1-7

**Body weights:** No treatment-related effects

**Food consumption:** No treatment-related effects.

**Local toxicity:** No treatment-related effects

**Toxicokinetics:** There were no differences in the serum concentrations of CG5503 on Dosing Days 1 and 14, and therefore no evidence of accumulation. Oral administration at 15 mg/kg/day resulted in extremely low serum concentrations, suggesting first-pass metabolism. The oral bioavailability was <1%. The results of the toxicokinetic evaluation after IV dosing on Day 14 are presented in the following table (provided from the original NDA submission):

**APPEARS THIS WAY  
ON ORIGINAL**