CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-304

SUMMARY REVIEW

11/20/08

Summary Basis for Regulatory Action

Date	November 20, 2008
From	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # Supp #	N[ ]
Applicant Name	Johnson & Johnson Pharmaceutical Research & Development
Proprietary / Established (USAN) Names	TBD Tapentadol
Dosage Forms / Strength	Tablet 50 mg, 75 mg, 100 mg
Proposed Indication(s)	1. Relief of moderate to severe acute pain
Action:	*Approval*

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1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding tapentadol and the reader should refer to the reviews in the action package for a more detailed discussion. Tapentadol is a mu opioid agonist and also has norepinephrine reuptake inhibitor activity. Tapentadol is structurally related to tramadol and has similar pharmacological actions, however tapentadol has demonstrated abuse liability similar to hydromorphone. This will require scheduling for tapentadol (schedule II) unlike tramadol which is not scheduled.

As detailed in Drs. Shibuya, Fields, Rappaport and Norton's reviews, tapentadol has demonstrated efficacy in replicated adequate clinical trials. The safety profile appears typical for an opioid agent and also similar to tramadol in certain aspects. As such, if agreements can be made regarding labeling, I will recommend an approval action.

Efficacy

This has been thoroughly covered in Drs. Shibuya, Fields and Norton's reviews and I will not elaborate on their reviews. The evaluation for efficacy was demonstrated in two studies, 32 and 33. Study 32 was conducted in bunionectomy subjects evaluated with a Summed Pain Intensity Difference over 48 hours (SPID48). This study demonstrated clear efficacy, dose response and was supported by secondary endpoints.

Study 33 was conducted in subjects with degenerative joint disease of the hip or knee with efficacy evaluated by a SPID-5 days. Efficacy was again demonstrated and supported by secondary endpoints, although there was not demonstration of a dose response.

Safety

The safety profile for tapentadol is similar to other opioids and to tramadol. The most common AEs as stated in Dr. Shibuya's review are those typical of an opioid and were nausea, dizziness, vomiting, somnolence, constipation and pruritus.

There are other safety concerns to be considered and the product should have labeling to reflect these concerns and uncertainties. Seizures were observed in rats at high doses and in dogs at clinically relevant doses. During clinical trials, there was one case in which a Phase 1 study participant had a seizure, but this was confounded as discussed in Dr. Shibuya's review. I note that subjects at risk for seizures were excluded from the trials and labeling should reflect this concern and uncertainty regarding how subjects at risk may react if given tapentadol.

Another safety concern is in regard to the norepinephrine reuptake activity of this NME as this activity poses a concern of possible serotonin syndrome if used concomitantly with MAOIs, SSRIs etc. I also note that drug combinations which may pose an interaction problem were prohibited in the clinical trials and this should also be reflected in labeling.

Finally, abuse liability studies demonstrated liability similar to hydromorphone. This has sparked interest in requiring a medication guide. This probably has merit as it should be instructed that, even though this is similar to tramadol, it has much greater abuse liability issues.

Conclusions and Recommendations

Tapentadol has demonstrated efficacy for the relief of moderate to severe pain. It also has a safety profile that has both the characteristics of a typical opioid and tramadol. Tapentadol has the risks briefly outlined above, and labeling should reflect these concerns. Tapentadol was not taken to an Advisory Committee meeting as there are several previously approved agents in the opioid class of drugs and evaluation of the safety data did not reveal particular safety issues unexpected for this class or of tramadol-like agents. Additionally, design and results of the efficacy trials did not pose particular concerns. I agree that a medication guide is probably appropriate for tapentadol.

I believe, that with proper labeling, the risk: benefit considerations of tapentadol would allow marketing. As such, I recommend an Approval action if proper labeling can be negotiated with the sponsor.

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/s/

Curtis Rosebraugh
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MEDICAL OFFICER

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FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

Summary Review for Regulatory Action

Date	November 16, 2008
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia and Rheumatology Products
Subject	Division Director Summary Review
NDA#	22-304
Applicant Name	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Date of Submission	January 22, 2008
PDUFA Goal Date	November 23, 2008
Proprietary Name / Established (USAN) Name	N/A Tapentadol hydrochloride
Dosage Forms / Strength	Immediate-release tablets, 50 mg, 75 mg and 100 mg
Proposed Indication	For the relief of moderate to severe acute pain
Recommended Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Ellen Fields, M.D.
Statistical Review	Jonathan Norton, Ph.D.; Dionne Price, Ph.D.; Thomas Permutt, Ph.D.
Pharmacology Toxicology Review	Kathleen Young, Ph.D.; Adam Wasserman, Ph.D.
CMC Review	John C. Hill, Ph.D.; Ali Al-Hakim, Ph.D.; Blair Fraser, Ph.D.
Microbiology Review	N/A
Clinical Pharmacology Review	David Lee, Ph.D.; Suresh Doddapaneni, Ph.D.
DDMAC	Michelle Safarik, PA-C
DSI	Antoine El-Hage, Ph.D.; Constance Lewin, M.D.
CDTL Review	Robert B. Shibuya, M.D.
OSE/DMEPA	Laura Pincock, Pharm.D.; Kellie Taylor, Pharm.D., M.P.H.; Carole Holquist, R.Ph.
OSE/DAEA	N/A
OSE/DRISK	Gita Akhavan-Toyserkani, Pharm.D.; Mary Dempsey; Claudia Karwoski, Pharm.D.
OSE/DEPI	N/A

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK= Division of Risk Management
DAEA=Division of Adverse Event Analysis
CDTL=Cross-Discipline Team Leader
DEPI= Division of Epidemiology

1. Introduction

Tapentadol HCl is a weak μ-opioid agonist and norepinephrine reuptake inhibitor developed for the treatment of acute, moderate to severe pain. Tapentadol is structurally similar to tramadol and has similar pharmacological properties. This product is an immediate-release formulation of tapentadol. [redacted] b(4)

2. Background

The sponsors had numerous interactions with the Agency during development. Agreement was reached on study design, study length, the statistical analysis plan, and the level of risk mitigation necessary for this novel opioid. Some of the efficacy studies included oxycodone as an active comparator. This was done primarily

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The sponsor has asked that the product be controlled under Schedule II of the Controlled Substances Act and that routine pharmacovigilance be the only additional risk mitigation strategy employed to address abuse liability. Based on the relatively low potency of the product and the fact that it is an immediate-release formulation, extensive risk management strategies to address abuse have not been required. However, a REMS was required due to the need for a MedGuide to inform patients of the risks associated with the use of this product.

3. CMC

The formulation consists of film-coated tablets The synthetic and manufacturing processes were determined to be robust by Dr. Hill. The different strengths b(4) are The release specifications have been determined to be acceptable by the CMC review team. The stability data support an expiration dating of 18 months. The sponsor has agreed to continue stability testing to more firmly establish their proposed shelf life.

4. Nonclinical Pharmacology/Toxicology

The nonclinical studies of tapentadol demonstrated notable toxicities including:

- convulsions in both rats and dogs,
- dose-related elevations in transaminases, alkaline phophatase and liver weights, with heptocellular hypertrophy and one instance of hepatic necrosis, and
- hERG channel inhibition at concentrations far greater than the maximum human dose, but with QT prolongation in both in vivo and in vitro pharmacology studies in dogs also at high doses.

Subjects at risk for the development of seizures were excluded from the clinical studies based on the findings in the animal studies.

Tapentadol did not demonstrate mutagenicity or clastogenicity in the Ames and mouse micronucleus tests, but the results of a CHO assay were equivocal. A two-year carcinogenicity study was, however, negative. While some fetal malformations were noted in the Segment II (Embryofetal Development) Study, Drs. Young and Wasserman concur with the sponsor that these abnormalities were due to maternal toxicity and not to a direct teratogenic effect of

tapentadol. No other significant abnormalities were documented in the reproductive toxicology studies.

5. Clinical Pharmacology/Biopharmaceutics

The proposed dosing regimen is 50 mg, 75 mg or 100 mg every 4 to 6 hours, with a single extra dose one hour following the first dose (a "reload" dose per the protocol). The sponsor submitted nine biopharmaceutics and twenty-two clinical pharmacology studies. The Clinical Pharmacology review team has determined that this product is BCS Class I. The product is dose linear for all doses and the oral bioavailability is 32% fasted and 42% fed. The $t_{1/2}$ is ~4.3 hours. Approximately 97% of the drug is metabolized in Phase 2 conjugation and excreted in the urine within 24 hours. The metabolites are not pharmacologically active and no relevant CYP interactions were demonstrated. Nor were there any clinically relevant pharmacodynamic interactions found in studies of tapentadol administered concomitantly with metoclopramide, omeprazole, probenecid, naproxen, ASA and APAP.

A Thorough QT Study demonstrated no QT prolongation. Pharmacokinetic parameters were similar between elderly and young adults, and there were no differences between Japanese and non-Japanese subjects. C_{max} and AUC values were ~20% higher in women than men, but this difference was no longer apparent after normalization for body weight. The C_{max} and AUC of tapentadol increased to a moderate degree with mild to moderate hepatic impairment, as did the $t_{1/2}$. Renal impairment did not affect the pharmacokinetics of tapentadol. While increasing renal impairment did result in increases in the C_{max} and AUC of the tapentadol-O-glucuronide metabolite, this metabolite is pharmacologically inactive.

6. Clinical Microbiology

No clinical microbiology data were necessary for this application.

7. Clinical/Statistical-Efficacy

The sponsor has submitted two studies to provide evidence of the efficacy of tapentadol, Study 32 and Study 33. Both studies were randomized, double-blind, active- and placebo-controlled, parallel-group trials comparing various doses of tapentadol to oxycodone and placebo. Study 32 was performed in patients with at least moderate pain following bunionectomy. If sufficient pain was reported within 9 hours post-surgery, the subjects were randomized and treated for 72 hours as inpatients with tapentadol 50 mg, 75 mg or 100 mg every 4 to 6 hours, or to oxycodone 15 mg or placebo every 4 to 6 hours. A single "reload" dose was allowed one hour after the first dose, but no rescue medication was permitted. The primary outcome analysis was the Summed Pain Intensity Difference over 48 hours (SPID48), based on the results of pain assessments employing an 11-point numerical rating scale. Missing data were imputed using an LOCF methodology. The results of the primary outcome analysis are summarized in the following table reproduced from page 36 of Dr. Field's review:

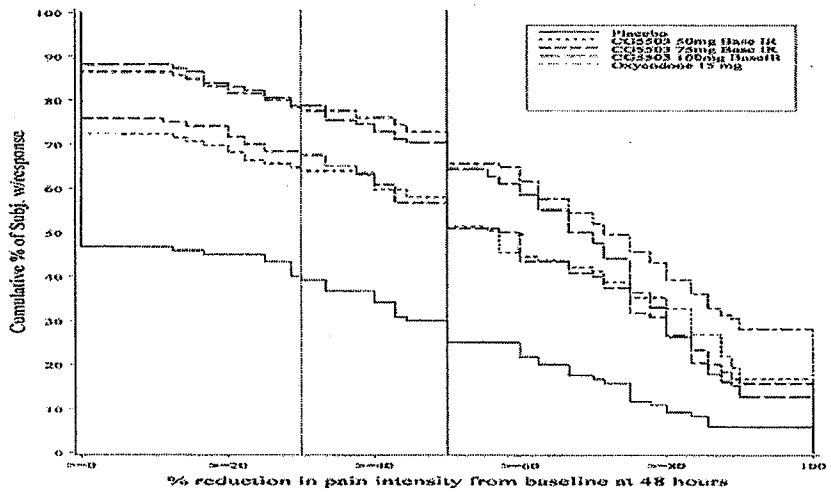
Table 12: Descriptive Statistics and Pairwise Comparison of SPID48 Using Hochberg Procedure-Primary Analysis, LOCF

	Placebo (N=120)	Tapentadol IR 50 mg (N=119)	Tapentadol IR 75 mg (N=120)	Tapentadol IR 100 mg (N=118)	Oxycodone HCl IR 15 mg (N=125)
0-48 Hours					
Mean (SD)	24.5 (120.93)	119.1 (125.86)	139.1 (118.93)	167.2 (98.99)	172.3 (110.86)
Median	43.4	127.6	131.3	158.5	170.6
(Range)	(-278;274)	(-185;402)	(-199;462)	(-94;408)	(-190;431)
LS Means (diff from placebo)	--	88.2	113.5	141.4	142.4
95% CI	--	60.71 to 115.59	86.12 to 140.81	113.98 to 168.90	115.28 to 169.47
Adjusted p-value vs. placebo[a]	--	<0.001	<0.001	<0.001	

[a] Based on analysis of covariance model with factors of treatment, center, and baseline pain intensity as a covariate. Adjusted p-values using Hochberg procedure. Oxycodone group is not included.
CSR R331333-PAI-3003 (KF5503/32), p. 86

All of the secondary analyses of the primary endpoint, including use of a BOCF imputation strategy, were supportive of the primary outcome. The secondary outcome measures were also supportive. The cumulative response curve below has been reproduced from page 40 of Dr. Field's review:

Figure 4: Cumulative Distribution of Responders at 48 Hours



Source: ▪ CSR R331333-PAI-3003 (KF5503/32), p. 90
Source: ▪ CSR R331333-PAI-3003 (KF5503/32), p. 90

In Study 33, patients with end-stage osteoarthritis of the hip or knee, who were candidates for replacement of the affected joint and who were currently at Step 2 or higher of the WHO Pain Ladder (combination opioid/non-opioid analgesic or opioid analgesic), were randomized to 10 days of treatment with either tapentadol 50 mg or 75 mg (titrated from 50 mg for the first two days), or oxycodone 10 mg or placebo, each on an every 4 to 6 hour regimen. No rescue or "reload" was permitted. The primary outcome analysis was a 5-Day SPID, based on the results of pain assessments employing an 11-point numerical rating scale. Double blind dosing was continued, however, for up to ten days to collect more accurate safety data over a time period that OA patients may well continue to take this type of product in the postmarketing period. The results of the primary outcome analysis are summarized in the following table reproduced from page 61 of Dr. Field's review:

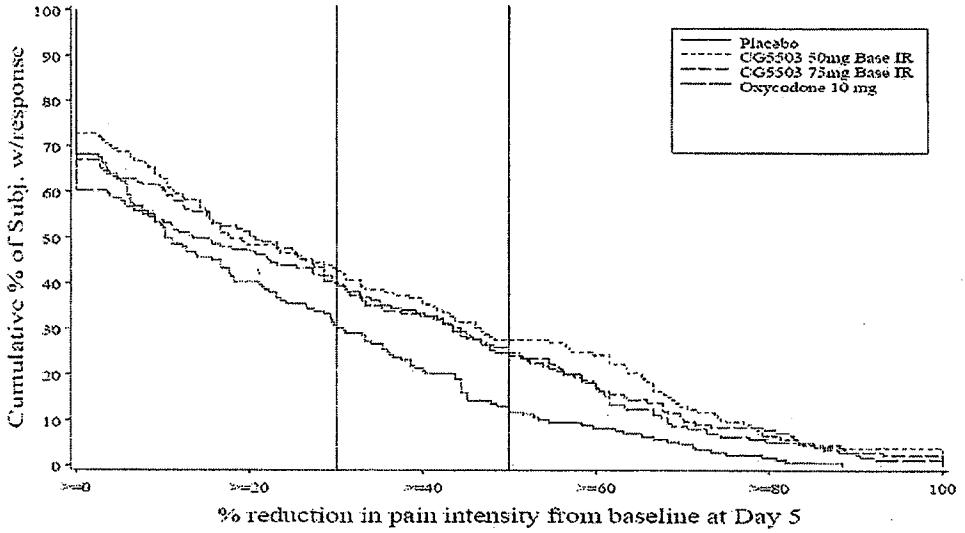
Table 23: Descriptive Statistics and Pairwise Comparison of SPID at Day 5 (LOCF)

	Placebo (N=169) n (%)	Tapentadol IR 50 mg (N=153) n (%)	Tapentadol IR 75 mg (N=166) n (%)	Oxycodone HCl IR 10 mg (N=171) n (%)
Day 1-5				
N	169	153	166	171
Mean (SD)	130.6 (182.77)	229.2 (228.92)	223.8 (217.76)	236.5 (222.82)
Median	86.6	164.1	210.2	206.7
(Range)	(-358;695)	(-480;881)	(-308;823)	(-268;884)
LS Means (diff from placebo)	--	101.2	97.5	111.9
95% CI	--	54.58 to 147.89	51.81 to 143.26	66.49 to 157.38
Raw p-value	--	<0.001	<0.001	<0.001
Adjusted p-value using Hochberg	--	<0.001	<0.001	--

Source: Clinical Study Report R331333-PAI-3002 (KF5503/33), p. 85

Again, all of the secondary analyses of the primary endpoint, including use of a BOCF imputation scheme, were supportive of the primary outcome. However, no dose-response was seen between the 50 mg and 75 mg doses in this study. The secondary outcome measures were also supportive. The cumulative response curve below has been reproduced from page 64 of Dr. Field's review:

Figure 7: Cumulative Distribution of Responder rates Based on Percent Change from Baseline in Pain Intensity at Day 5



Source: Clinical Study Report R331333-PAI-3002 (KF5503/33), p. 89

DSI conducted routine inspections and found data irregularities at two clinical sites. However, Dr. Norton assessed the data from these two sites and found that they were similar to the data from the other sites.

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8. Safety

The safety database for this application consisted of 3,515 subjects treated with one or more doses of tapentadol. Most of the subjects were treated for 10 days or less, but 454 patients in

the Phase 2/3 studies were treated for greater than 45 days. There was one death reported in a subject treated in an ongoing study of immediate-release tapentadol. Treatment assignment remains blinded for this study; however, this death did not appear to be causally related to the study drug. There have been four deaths reported from ongoing studies of the extended-release tapentadol product. None of these deaths occurred during treatment and three of the deaths did not appear to be causally related to study drug. The fourth death, due to cardiac arrest, is being further evaluated by the sponsor at this time and the treatment assignment remains blinded.

I concur with the following statements from page 13 of Dr. Shibuya's review:

> Dr. Fields reviewed each death, non-fatal serious adverse event, and adverse event leading to discontinuation in detail. While some of these events could be reasonably attributed to treatment with tapentadol such as ileus, lethargy, etc., none of the deaths, serious adverse events, or adverse events leading to discontinuation were [sic] unexpected for an opioid agonist used in an acute setting.
>
> With regard to the common AEs, generally, the safety profile is consistent of that of an opioid agonist with the most common AEs being nausea, dizziness, vomiting, somnolence, constipation, and pruritis.

There was one seizure reported in a subject in a Phase 1 study. This subject failed to report a history of epilepsy at screening and experienced a generalized tonic-clonic seizure three days after a single 150-mg dose of tapentadol. He later acknowledged having discontinued his anticonvulsant medication a few months before entering the study. While there were a small number of subjects treated with tapentadol with elevated liver enzymes, the rates of enzyme elevation were not above those seen with oxycodone or placebo, and there were no cases of enzyme elevations concurrent with clinically relevant bilirubin elevations.

An abuse liability study demonstrated a liability similar to hydromorphone. In a study in which subjects were discontinued from treatment without a tapering of dose, a modest percentage of the subjects experienced symptoms consistent with withdrawal. There were no overdoses and there was no evidence of abuse or diversion during the clinical studies. I concur with the clinical review team and the DRISK review team that the abuse risk for tapentadol appears to be high and that a Schedule II classification is appropriate.

9. Advisory Committee Meeting

This application was not taken before an advisory committee as tapentadol is not a "first-in-class" drug and there were no concerning safety signals; nor was there any concern regarding the data provided to support evidence of the product's efficacy.

10. Pediatrics

The sponsor has requested deferral of pediatric studies until a reasonable safety experience in adults has occurred post-marketing. I concur with the review team that this is appropriate.

11. Other Relevant Regulatory Issues

The initial choice of trade name was rejected by the DMEPA review team due to possible name confusion concerns. The product may be approved under the generic name until an acceptable trade name has been determined. There are no other unresolved regulatory issues.

12. Labeling

The review team proposed a number of labeling changes to the package insert and to the carton and container labeling which will need to be resolved prior to approval.

13. Decision/Action/Risk Benefit Assessment

- Recommended Regulatory Action

  I recommend approval, pending agreement on product labeling.

- Risk Benefit Assessment

  The sponsor has provided adequate evidence to support the efficacy, safety and quality of their product. There appear to be no unusual concerns for this product compared to other similar analgesics. The risk of abuse has been appropriately addressed as discussed below. The pro-convulsive activity of tapentadol does support limitation of the product's use in at risk patients. I concur with Dr. Shibuya that consideration should be given to raising "predisposition to seizure" to a Contraindication.

- Recommendation for Postmarketing Risk Management Activities

  Standard pharmacovigilance and a Schedule II classification should be adequate to mitigate the risk of abuse for this product. Should signals of abuse be found postmarketing, more extensive risk management strategies may need to be implemented. A REMS has been required due to the need for a MedGuide to inform patients of the risks associated with the use of tapentadol.

- Recommendation for other Postmarketing Study Commitments

  No postmarketing study commitments are required for this application other than the pediatric program which will be deferred until a reasonable safety profile has been established in adults in the postmarketing period.

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Bob Rappaport
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