CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-304

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	23 September 2008
From	Robert B. Shibuya, M.D., Clinical Team Leader
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA [redacted] b(4)
Applicant	Johnson & Johnson Pharmaceutical Research & Development
Date of Submission	22 January 2008
PDUFA Goal Date	22 October 2008
Proprietary Name / Established (USAN) names	To be determined/Tapentadol HCl
Dosage forms / Strength	Tablet, 50, 75, 100 mg
Proposed Indication	1. Relief of moderate to severe acute pain
Recommended:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Primary Medical Officer Review	Ellen W. Fields, M.D., MPH
Statistical	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.
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.
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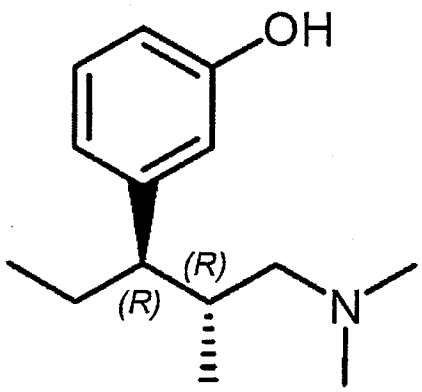
OSE/DRISK	Gita Akhavan-Toyserkani, PharmD Mary Dempsey Claudia Karwoski, PharmD

1. Introduction

Tapentadol is a New Molecular Entity (NME) with weak mu opioid agonist activity and norepinephrine uptake activity. It was developed under IND 61,345 for the management of acute moderate to severe pain. The chemical formula for tapentadol is $C_{14}H_{23}NO*HCl$ and the chemical structure is shown on the next page.



. HCl

For this immediate-release tablet, the applicant, Johnson & Johnson Pharmaceutical Research & Development, is seeking the indication of "the relief of moderate to severe acute pain." At this time, the applicant has not provided an acceptable tradename. Therefore, the product will be referenced as "tapentadol" throughout this review. Proposed strengths are 50, 75, and 100 mg.

At various meetings, including a Pre-IND Meeting, the End-of-Phase 2 Meeting, and the Pre-NDA Meeting, the Division described what efficacy and safety data would support approval. The Division indicated that two multiple-dose studies of at least 2-5 days duration would be required. The applicant felt that the pain in most acute pain scenarios is not of sufficient duration to demonstrate analgesia over 5 days. Therefore, the applicant proposed studying end-stage degenerative joint disease in one of the adequate and well-controlled studies. The Division agreed with this proposal.

The issue of missing data was addressed on several occasions and the Division indicated that, due to the phenomenon of differential dropout, the applicant must use a conservative imputation scheme. The applicant decided to use Last Observation Carried Forward (LOCF), a non-conservative imputation scheme, as the primary method to account for missing data. The applicant included Baseline Observation Carried Forward (BOCF), a conservative imputation scheme, in the statistical analysis plan and agreed that the BOCF analysis must confirm any positive LOCF result. In the Agency review of this NDA, the efficacy studies were carefully assessed and reanalyzed to address this issue.

Tapentadol is structurally related to tramadol (Ultram) and has similar pharmacological effects. Among typical opioid effects, tramadol, particularly in combination with monoamine oxidase inhibitors, is associated with seizures and serotonin syndrome. The safety assessment for tapentadol, in addition to the scrutiny afforded a NME, also assessed these specific areas of concern.

In addition, as an opioid, given the issues of prescription drug abuse, we have given careful consideration to risk mitigation for tapentadol. While tapentadol is likely to be classified in Schedule II, because of tapentadol's relative lack of potency and immediate-release formulation (such that an individual dosage unit is unlikely to cause significant harm to an individual), at this time, tapentadol immediate-release tablets will not be deemed to require a Risk Evaluation and Mitigation Strategy (REMS) and that routine pharmacovigilance and Schedule II controls should suffice to manage risks.

2. Background

Tapentadol is an immediate-release weak mu opioid agonist with analgesic activity for which the applicant is seeking an indication of the management of acute moderate to severe pain. As will be discussed in later sections of this review, the drug appears efficacious and the safety profile appears typical for an opioid. All review disciplines are recommending approval. The Office of Surveillance and Epidemiology felt that routine pharmacovigilance was appropriate and opined that the Applicant's post-marketing safety surveillance was appropriate.

3. CMC/Device

The CMC review was conducted by John Hill, Ph.D. Tapentadol, immediate-release tablets are film-coated and undergo a[ ] Both the synthetic process and manufacturing process were felt to be robust by Dr. Hill. The product is[ ] Dr. Hill's initial CMC review noted several deficiencies including contact information, limit of detection/quantitation for the dissolution method, method validation for the[ ] test, and a letter of authorization to a DMF. The applicant's response to an Information Request was adequate and Dr. Hill and Dr. Ali Al-Hakim, Chief, Branch II, ONDQA, are recommending approval from the CMC perspective. The review of the Environmental Assessment was conducted by Ruth Ganunis who found the Applicant's assessment acceptable.

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4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology Review was conducted by Kathleen Young, Ph.D. with a secondary review by Adam Wasserman, Ph.D, Supervisory Pharmacologist.

Tapentadol was subjected to the required battery of nonclinical testing for a NME. Key findings in the non-clinical program are summarized below.

- Tapentadol is a mu-opioid agonist with some sigma (S2) activity and norephinephrine reuptake inhibitor activity. The molecule is structurally related to tramadol.
- Notable toxicities (beyond the expected, opioid-related CNS, GI, and respiratory effects) included:

- Tapentadol caused convulsions in rats at very high IV doses (15 mg/kg). These effects in the rat were observed after the parent drug and metabolites had cleared. This finding was not further evaluated by the applicant. Convulsions were noted in dogs, dosed subcutaneously and orally, at doses as low as 40 mg/kg/day. The convulsions were observed across several studies of various chronicities. There was no evidence of tolerance to the convulsant effect observed. Because of these nonclinical findings, humans at risk for seizure were excluded from participation in clinical trials with tapentadol.
- Dose-related, reversible hepatotoxicity was observed, manifested by elevations in transaminases, alkaline phosphatase, and liver weights with hepatocellular hypertrophy and one instance of hepatic necrosis. Rats were more sensitive to tapentadol-associated hepatotoxicity than dogs. The hepatotoxicity was noted at fairly high doses in rats (150 mg/kg/day).
- The other non-opioid-related target organ was the cardiovascular system. Tapentadol caused hERG channel inhibition at high concentrations (approximately 70-times the maximum Cmax of the maximum human dose) and it showed QT prolongation in *in vitro* and *in vivo* dog pharmacology studies, again at high doses/concentrations. This activity has been associated with norepinephrine reuptake inhibition.

- Tapentadol was negative in the Ames and mouse micronucleus test. It was equivocal in the CHO assay. It is important to note that a 2-year carcinogenicity study was negative.
- With regard to reproductive toxicity, the only finding that exceeded historical control rates was ablepharia (absence of the eyelids) in Himalayan rabbits although the remainder of the studies were negative.

Drs. Young and Wasserman have recommended approval for this product from the Pharmacology/Toxicology perspective.

5. Clinical Pharmacology/Biopharmaceutics

The primary Clinical Pharmacology and Biopharmaceutics (CP/B) review was conducted by David Lee, Ph.D. with supervisory concurrence by Suresh Doddapaneni, Ph.D.

The applicant is seeking the approval of three strengths, 50, 75, and 100 mg. The dosing regimen is to be every 4-6 hours. The applicant wishes to add a provision for patients to take one extra dose of tapentadol one hour following the first dose ("reload").

To support this dosing and administration scheme as well as address routine clinical pharmacology issues, the applicant conducted an extensive Clinical Pharmacology and Biopharmaceutics program. In total, the applicant conducted nine biopharmaceutics studies providing information on absolute bioavailability, food effect, and dose linearity. Twenty-two clinical pharmacology studies were submitted providing data on metabolism, effects on the QT interval, special populations, drug-drug interactions, and pharmacokinetic/pharmacodynamic correlation. With regard to studies directly related to dosing and administration, there were six Phase 2 studies (single- and multiple-dose) in patients following third-molar extraction,

chronic non-cancer pain, and following bunionectomy that provided support for the dose range, dosing interval, and concept of "reload."

Key findings from the CP/B program follow.

- The Agency agreed with the applicant that this product is BCS class I (highly soluble, highly permeable).
- The capsule formulation used in Phase 1/2 was bioequivalent to the to-be-marketed film-coated tablet used in Phase 3.
- General clinical pharmacology information:
  - Absolute oral bioavailability was 32% (fasted) and 42% (fed).
  - Food caused a 16% increase in C_{max} and a 25% increase in AUC.
  - Tapentadol is dose-linear from 50 to 175 mg.
  - The $t_{1/2}$ is ~4.3 hours.
  - The accumulation factor is 1.6 when dosed every 6 hours.
  - The clearance is 1530 +/- 177 mL/min.
- Metabolic information:
  - Approximately 97% is metabolized and excreted in urine and ~95% is excreted within 24 hours.
  - The predominant metabolic pathway is Phase 2 conjugation of the parent drug (55% tapentadol-O-glucoronide and 15% tapentadol-O-sulfate).
  - There is a lesser amount of Phase 1 metabolism (13% to N-desmethyl tapentadol via CYP2C9 and 2% to hydroxy tapentadol via CYP2D6).
  - The metabolites are not pharmacologically active.
  - No clinically relevant inhibition of 1A2, 2C9, 2C19, 2D6, or 3A4 was observed.
  - No clinically relevant induction of 1A2, 2C9, and 3A4 was observed.
  - Tapentadol is neither a substrate or inhibitor of P-glycoprotein.
- Drug-drug interactions
  - An 80 mg dose of tapentadol was tested in conjunction with metoclopramide, omeprazole, probenecid, naproxen, acetylsalicylic acid, and acetaminophen. No clinically relevant interactions were identified.
- As reported by Christine Garnett, Ph.D., a thorough QT study using 100 or 150 mg dosed every 6 hours (moxifloxacin control) showed no QT effect.
- Special populations information:
  - The PK parameters were similar in elderly and other healthy adults.
  - There did not appear to be any difference in the PK of Japanese or non-Japanese subjects.
  - With regard to gender, women in general had ~20% higher C_{max} and AUC values than men. After bodyweight normalization, this difference disappeared.
  - Hepatic impairment
    - The C_{max} of tapentadol increased 1.4 and 2.5-fold in subjects with mild and moderate hepatic impairment, respectively.
    - The AUC of tapentadol increased 1.7 and 4.2-fold in subjects with mild and moderate hepatic impairment, respectively.

- The elimination half-life increased 1.4-fold in subjects with moderate hepatic impairment.
- The applicant did not test the drug in subjects with severe hepatic impairment.

- Renal impairment
  - There were no effects observed in the pharmacokinetics of the tapentadol moiety with perturbations in renal function.
  - However, C_{max} and AUC for the tapentadol-O-glucoronide metabolite increased with increasing renal impairment (1.2- and 5.5-fold for C_{max} and AUC in severe renal impairment).

Drs. Lee and Doddapaneni have recommended approval for this product from the Clinical Pharmacology perspective.

6. Clinical Microbiology

This section is not applicable since this is not an antimicrobial product.

7. Clinical/Statistical- Efficacy

The primary medical review was conducted by Ellen W. Fields, M.D., MPH, Clinical Team Leader and the primary statistical review was conducted by Jonathan Norton, Ph.D. Please see Dr. Fields' and Norton's reviews for further details regarding the clinical development program.

During development, tapentadol, in both this immediate-release, acute pain formulation and an extended-release, chronic pain formulation was the subject of multiple meetings with the Division. The original sponsor for this moiety, Grunenthal, is a German company and has been working closely with the European authorities to affect an approval in the EU.

In these meetings, it became clear that Grunenthal/J&J were not going to be able to exactly meet the expectations of both the European authorities and FDA in that, according to the applicant, the EMEA wanted ar[ ] [ ] b(4)

However, for this immediate-release, acute pain formulation, certain criteria for clinical trials were made clear by FDA. Over the course of the clinical development program, Grunenthal/J&J agreed with the following:

- Efficacy must be demonstrated in at least two adequate and well-controlled, multiple-dose studies.
- A flexible dosing regimen of every 4-6 hours was acceptable if the clinical trial data contained sufficient detail in the dosing times to support this notion.
- Again, provided that the clinical trial data were of sufficient detail and supported the safety and efficacy of the "reload," the Division would consider adding the "reload" concept into the Dosing and Administration section of the product labeling.

- While the protocol may use LOCF as the primary imputation scheme, a conservative imputation scheme such as Baseline Observation Carried Forward (BOCF) must support the primary analysis in order for the study to be perceived as positive.
- Efficacy must be demonstrated over 3-5 days. Because many commonly used acute pain scenarios (bunionectomy, third-molar extraction) resolve by 5 days, alternative painful scenarios may be acceptable for study.
- The relevance of the positive control (oxycodone) will be a review issue. [ ] [ ] b(4)

In the context of these agreements, the applicant has submitted two studies to support a finding of efficacy. Please see Dr. Field's excellent review for further details regarding the pivotal efficacy studies.

Study R331333PAI3003 (J&JRD)/KF5503/32 (Grunenthal) will be referenced as "Study 32" in this review. Study 32 was a randomized, double-blind, active- and placebo-controlled, parallel-group study in patients with at least moderate pain following bunionectomy.

Briefly, patients who had undergone an elective, unilateral first metatarsal bunionectomy and had pain of at least 4/10 following surgery and resolution of surgical anesthesia were eligible. In the context of the seizures observed in the nonclinical program, it is important to note that patients with a history of seizure disorder or those at risk of seizure (history of mild or moderate traumatic brain injury, stroke, TIA, or brain neoplasm within one year or history of severe brain injury, unconsciousness > 24 hours, posttraumatic amnesia > 24 hours within 15 years) were consistently excluded from clinical trials with tapentadol.

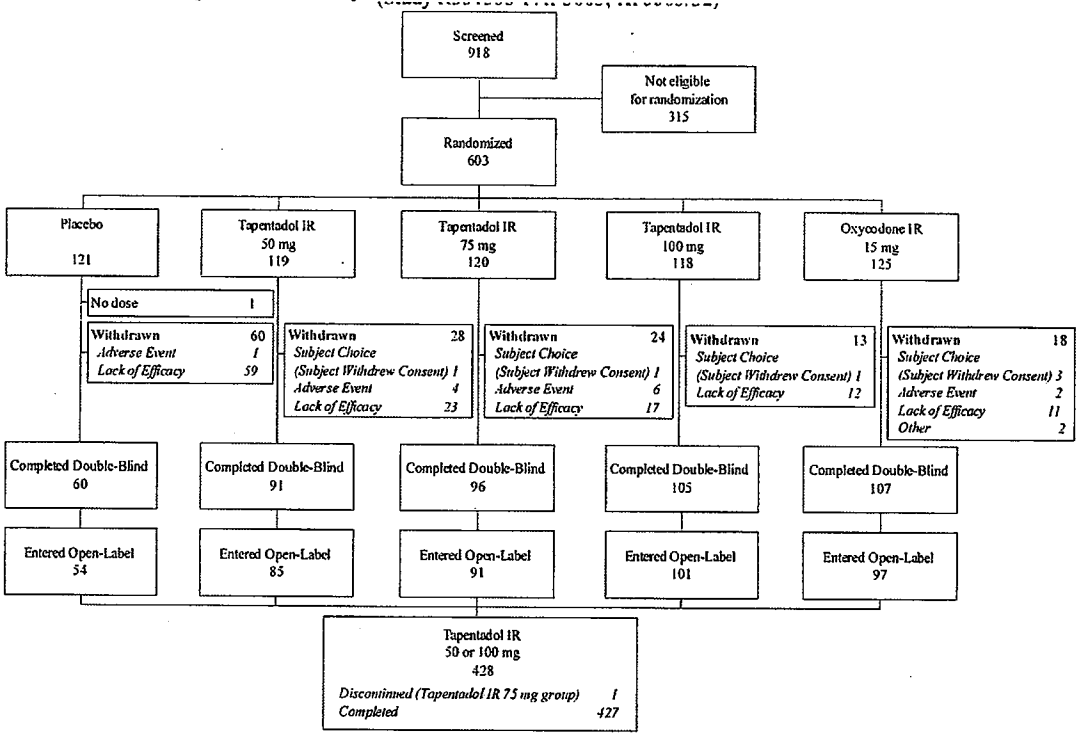
After screening and surgery, if sufficient pain was reported within 9 hours of surgery, patients were randomized and treated for a scheduled duration of 72 hours as inpatients. Patients were randomized to one of the following five treatments:

- Tapentadol, 50 mg Q 4-6 hours or
- Tapentadol, 75 mg Q 4-6 hours or
- Tapentadol, 100 mg Q 4-6 hours or
- Oxycodone, 15 mg Q 4-6 hours or
- Placebo

No rescue was to be permitted although a "reload" of one additional dose, one hour following the first dose only was permitted. If rescue was used, patients were to be dropped from the study. Patients were followed with pain assessments (11-point NPRS for intensity, 5-point NRS for relief, patient global, and two-stopwatch) and adverse event monitoring. The duration of double-blind dosing was to be 72 hours and the protocol provided for a voluntary, 9-day open-label extension.

A total of 918 patients were screened and 603 were randomized. Subject disposition is summarized in Figure 1, from Dr. Fields' review.

Figure 1: Patient disposition, Study 32



Predictably, given the fact that rescue was not permitted, the dropout rate was highest in the group randomized to placebo (~50%) and the dropouts almost universally dropped out due to lack of efficacy (59/60). The dropout rates ranged from 11-24% in the other arms and had much lower incidences of lack of efficacy (10-19%). Dr. Fields found that the demographic and baseline characteristics were reasonably balanced across study groups except the time from anesthesia stop to first dose of study drug which was shorter for the oxycodone group (mean 1.9 hrs) than the other groups (~2.5 hrs).

The primary efficacy endpoint was the Summed Pain Intensity Difference over 48 hours (SPID48). The analysis was conducted on the Intention-To-Treat population, defined as all randomized patients who received at least one dose of study drug and had a baseline pain intensity score. Missing data were imputed using a LOCF scheme.

The summary statistics for the primary endpoint are shown in this table from Dr. Fields' review below.

Table 1: Primary efficacy analysis, Study 32

	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	

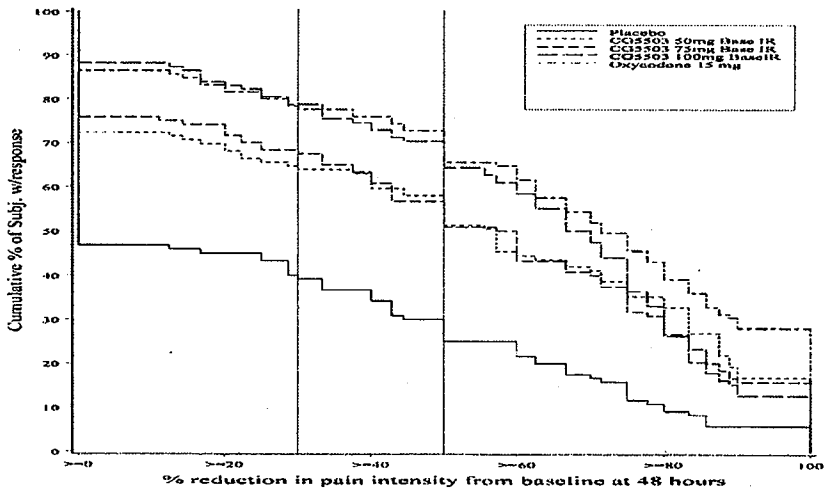
[a] Based on analysis of covariance model with factors of treatment, center, and baseline pain intensity as a covariate. Adjusted p-values using Hochberg procedure. Oxycodone group is not included.

As Dr. Fields notes, the tapentadol-treated groups separated from placebo and there was reasonable dose response observed between the tapentadol-treated patients.

Using alternative imputation schemes [BOCF and Worst Observation Carried Forward (WOCF)] as well as various mathematical permutations of the pain scores (responder status, SPID over 12, 24, and 72 hours, etc.) all analyses supported the primary efficacy analysis.

Secondary endpoints for Study 32 included time to first dose of rescue, responder status, and two-stopwatch data. The secondary endpoints also supported the finding of efficacy for tapentadol and tended to show a dose response between the tapentadol doses investigated. An example of one of the secondary endpoints is the continuous responder analysis from Dr. Fields' review (Figure 2).

Figure 2: Continuous responder analysis, Study 32



With regard to the applicant's concept of "reload," a one-time-only second dose of study drug, one hour after the first dose, I refer the reader to Dr. Norton's review (page 34). Dr. Norton notes that, predictably, the "reloaders" had worse pain outcomes since the patients who reloaded were still experiencing significant pain following the first dose. However, Dr. Norton concludes that the data following the "reload' dose suggest that the reload provided benefit.

The applicant's statistical analysis, including the reanalysis using conservative imputation schemes, was confirmed by Dr. Norton.

Study R331333PAI3002 (J&JRD)/KF5503/33 (Grunenthal) will be referenced as "Study 33" in this review. Study 33 was a randomized, double-blind, active- and placebo-controlled, parallel-group study in patients with pain in the setting of end-stage degenerative joint disease of the hip or knee. This patient population was selected because the applicant did not feel that the usual pain scenarios employed in clinical trials would be painful for an adequate duration to meet the Division's requirement of at least 3-5 days.

Briefly, eligible patients carried a clinical diagnosis of osteoarthritis of the hip or knee that were candidates for replacement of the affected joint and were currently at Step 2 or higher in the WHO pain ladder (combination opioid/non-opioid analgesic or opioid analgesic). Again, patients at risk for seizure were specifically excluded.

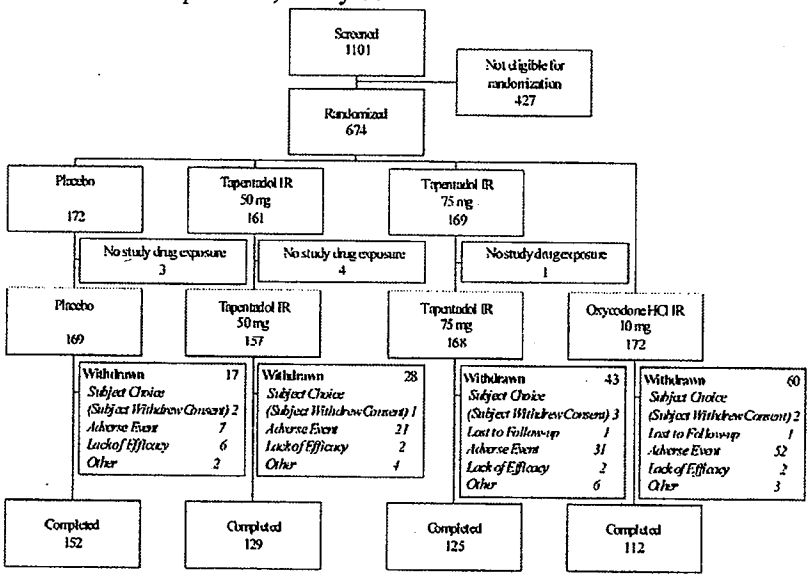
Eligible patients were randomized to one of four groups:

- Tapentadol, 50 mg Q 4-6 hours or
- Tapentadol, 75 mg Q 4-6 hours (uptitrated from 50 mg for the first 2 days) or
- Oxycodone, 10 mg Q 4-6 hours or
- Placebo

Again, no rescue was to be permitted and if rescue was used, patients were to be dropped from the study. No reload was permitted in this study. Patients were followed with pain assessments (11-point NPRS for intensity, 5-point NRS for relief, patient global) and adverse event monitoring. The duration of double-blind dosing was to be 10 days.

A total of 1,101 patients were screened and 674 were randomized. Subject disposition is summarized in Figure 3, from Dr. Fields' review.

Figure 3: Patient disposition, Study 33



Interestingly, the placebo group had the highest percentage of study completers (90%) compared to 65-82% in the other groups. The most common reason for early discontinuation was adverse event in the active arms. Dr. Fields found that the demographic and baseline characteristics were reasonably balanced between treatment groups.

The primary efficacy endpoint was the SPID-5 days using a LOCF imputation scheme and an ITT population definition identical to that used in Study 32. The summary statistics for the SPID-5 days is summarized in Table 2, from Dr. Fields' review.

Table 2: Summary Statistics, SPID-5 days, Study 33

	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	--

There was a statistically significant difference between the treatment groups and placebo. The data were also analyzed using BOCF and found to be rugged. However, it is interesting to note that no dose-response between the 50 and 75 mg doses of tapentadol was observed. Dr. Norton confirmed the analyses for Study 33.

The secondary efficacy analyses also supported the primary. Again, from Dr. Fields' review, Table 3 summarizes the secondary efficacy endpoints for Study 33.

Table 3: Secondary efficacy endpoints, Study 33

	Tapentadol IR 50mg (N=153)	Tapentadol IR 75mg (N=166)	Oxycodone HCl IR 10mg (N=171)
5-day SPID (LOCF)			
LS Means diff. from placebo (95% CI)	**101.2 (54.58, 147.89)**	**97.5 (51.81, 143.26)**	**111.9 (66.49, 157.38)**
Adjusted p-value vs. placebo[a, b]	**<0.001**	**<0.001**	--
Unadjusted p-value vs. placebo[a]	--	--	<0.001
5-day SPID (BOCF)[a,c]	<0.001	<0.001	--
5-day SPID (WOCF)[a]	<0.001	<0.001	<0.001
Two-part model on % change NRS and drop-out[d]	0.003	<0.001	<0.001
Pain assessment ≥30% improved at Day 5[e]	0.028	0.033	0.091
Pain assessment ≥50% improved at Day 5[e]	0.003	0.002	0.007
Distribution of responders at Day 5, Gehan test	0.011	0.107	0.626
Distribution of responders at Day 5, Log-rank test	<0.001	0.003	0.016
Distribution of responders at Day 5, Van Der Waerden test	0.005	0.070	0.503
Time to first rescue medication [c,f]	0.626	0.626	0.142
2-day SPID (LOCF)[a]	<0.001	<0.001	<0.001
10-day SPID (LOCF)[a]	<0.001	<0.001	<0.001
5-day TOTPAR (LOCF)[a]	<0.001	<0.001	<0.001
5-day SPRID (LOCF)[a]	<0.001	<0.001	<0.001
Patient Global Impression of Change[g]	<0.001	<0.001	0.005

[a] Based on analysis of covariance model with factors of treatment, pooled center, and baseline pain intensity as a covariate.
[b] P-values adjusted for multiplicity using Hochberg procedure.
[c] P-values for tapentadol groups are adjusted for multiplicity using Hochberg procedure. P-value for oxycodone group is not adjusted for multiplicity. ANCOVA model includes all treatment groups.
[d] For percent change NRS on Day 5 (observed case): ANCOVA model includes treatment, pooled center as factors and baseline pain score as a covariate. For discontinuation: Logistic regression model includes treatment as a factor and baseline pain score as a covariate.
[e] P-value based on Generalized Cochran-Mantel-Haenszel test for general association controlling for pooled center.
[f] Log rank test stratified with pooled center.
[g] P-value based on Generalized Cochran-Mantel-Haenszel test for row mean scores differ controlling for pooled center.
Higher value in SPID indicates greater pain relief.
Higher value in TOTPAR, SPRID indicates greater pain relief.

EFFICACY CONCLUSIONS

The applicant has submitted two adequate and well-controlled studies that showed that tapentadol, dosed at strengths of 50 to 100 mg every 4-6 hours, provided analgesia compared to placebo. The post-bunionectomy study is undoubtedly pertinent to the proposed indication. In conjunction with the six Phase 2 studies in other conventional acute and chronic pain

populations and the study done in patients with OA, it is clear that tapentadol is an effective analgesic. "Reload" appeared to provide benefit to patients who experienced inadequate analgesia following the first dose of tapentadol.

8. Safety

This is a high-level summary of the detailed review conducted by Dr. Fields for this New Molecular Entity. This section focuses on adverse events that were observed in the nonclinical program and those predicted because of the structural and pharmacological similarity of tapentadol to tramadol. Please see Dr. Fields' review for details.

The applicant submitted a safety database consisting of 3,515 subjects and patients who were dosed with one or more doses of tapentadol. The exposed populations have included healthy volunteers, post-operative orthopedic and dental pain, and chronic, non-malignant pain. The safety database size exceeds the ICH E1 recommendations for a NME.

Table 4, following, summarizes the numbers of subjects and patients treated by duration of treatment.

Table 4: Duration of therapy with tapentadol, placebo, and oxycodone, Phase 2/3

Duration of treatment, n (%)	Tapentadol	Placebo	Oxycodone
N	2178	619	675
1 day	481 (22)	191 (31)	141 (21)
≥2-3 days	586 (27)	199 (32)	192 (28)
>3-10 days	534 (25)	228 (37)	213 (32)
>10-45 days	123 (6)	1 (<1)	25 (4)
>45 days	454 (21)	0	104 (15)

Source: ISS, 4 Month Safety Update, page 96 (reformatted)

Table 4 shows that the vast majority of the patients were treated for 10 days or less although there is a substantial proportion (21%) who were treated for more than 45 days.

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 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. The common adverse events are summarized in Table 5 from Dr. Fields' review.

Table 5: TEAEs in at least 3% of patients in the Phase 2/3 multiple-dose, double-blind data set

System organ class Preferred term	Placebo (n=619) n (%)	"All" Tapentadol IR (n=2178) n (%)	"All" Oxycodone IR (n=675) n (%)
Total no. subjects With TEAEs	11 (2)	243 (11)	113 (17)
Nervous system disorders	5 (1)	105 (5)	53 (8)
Dizziness	3 (<1)	57 (3)	27 (4)
Somnolence	1 (<1)	28 (1)	15 (2)
Headache	1 (<1)	19 (1)	8 (1)
Lethargy	0	7 (<1)	0
Gastrointestinal disorders	5 (1)	95 (4)	82 (12)
Nausea	4 (1)	51 (2)	46 (7)
Vomiting	1 (<1)	30 (1)	35 (5)
Constipation	0	13 (1)	18 (3)
Diarrhoea	0	10 (<1)	0
Dry mouth	0	7 (<1)	0
Abdominal pain	0	4 (<1)	3 (<1)
Psychiatric disorders	3 (<1)	48 (2)	11 (2)
Confusional state	0	10 (<1)	1 (<1)
Insomnia	1 (<1)	8 (<1)	2 (<1)
Euphoric mood	0	6 (<1)	1 (<1)
Depressive symptom	0	5 (<1)	0
Anxiety	0	5 (<1)	0
Hallucination, visual	1 (<1)	4 (<1)	2 (<1)
General disorders and administration site conditions	1 (<1)	37 (2)	12 (2)
Fatigue	1 (<1)	14 (1)	5 (1)
Irritability	0	7 (<1)	2 (<1)
Chest discomfort	0	4 (<1)	0
Skin and subcutaneous tissue disorders	0	25 (1)	17 (3)
Pruritus	0	8 (<1)	11 (2)
Hyperhidrosis	0	5 (<1)	5 (1)
Pruritus generalised	0	5 (<1)	1 (<1)
Musculoskeletal and connective tissue disorders	1 (<1)	12 (1)	2 (<1)
Muscle spasms	0	4 (<1)	0
Respiratory, thoracic and mediastinal disorders	0	8 (<1)	0
Dyspnoea	0	4 (<1)	0

Dr. Fields found that there appeared to be dose-response for the severity of adverse events for nausea, dizziness, and somnolence.

Specific Safety Concerns for Tapentadol:

The specific safety concerns to be addressed include seizures, serotonin syndrome, hepatotoxicity, cardiotoxicity, and abuse/misuse/addiction/overdose.

Seizures

Seizures were observed in rats at high doses and dogs at clinically relevant doses.

There was one seizure reported in the tapentadol development program. This was a subject on a Phase 1 study who failed to report a history of epilepsy at screening. Three days following a 150 mg dose of tapentadol, he experienced a generalized tonic-clonic seizure. He reported that he had discontinued his anti-convulsant drug (valproic acid) a few months prior to his participation in the study.

No other seizures were reported although it is important to note that patients at risk for seizure were specifically excluded from clinical trials with tapentadol.

Serotonin Syndrome

The concomitant use of MAOIs, SSRIs, SNRIs, and TCAs was prohibited in the clinical trials because of concerns about serotonin syndrome. The safety database showed no cases of serotonin syndrome nor symptom/sign constellations suspicious for serotonin syndrome.

Hepatotoxicity

Clinical laboratory and histopathologic evidence of hepatotoxicity was observed in the nonclinical development program at high doses (150 mg/kg/day).

In the clinical development program, subjects and patients were monitored via standard hematology and clinical chemistry tests. The applicant considered the following hepatic laboratory abnormalities to be "potentially clinically important (high)."

- Alanine aminotransferraase >3x ULN
- Aspartate aminotransferrase >3x ULN
- Gamma glutamyltransferrase >3x ULN
- Total bilirubin >1.5x ULN
- Alkaline phosphatase >1.5x ULN
- Lactic dehydrogenase >1.5x ULN

Subjects and patients whose laboratory data met the "potentially clinically important" were identified. The crude counts and percentages of patients in the major treatment groups are summarized in Table 6.

Table 6: Subjects/Patients meeting criteria for elevated potentially clinically important hepatic laboratory abnormalities in multiple-dose, double-blind studies

Analyte	Placebo, n=602	Tapentadol, n=2113	Oxycodone, n=675
Alkaline phosphatase	1 (<1)	7 (<1)	2 (<1)
GGT	0	5 (<1)	1 (<1)
ALT	1 (<1)	3 (<1)	2 (<1)
AST	1 (<1)	2 (<1)	1 (<1)
Bilirubin	0	2 (<1)	1 (<1)

Table 6 shows that, for the potentially important elevations in hepatic markers, the rates were similar across the pooled treatment groups.

There were no cases of:

AST/ALT > 10x ULN or
AST/ALT > 3x ULN and alkaline phosphatase < LLN or bilirubin > ULN

Dr. Fields reviewed and summarized data from the five subjects/patients who discontinued due to abnormal liver function tests. In each case, a relationship to treatment with tapentadol was either unlikely or unclear due to exposure to multiple medications or the existence of hepatic laboratory abnormalities at baseline.

The shift tables showed no evidence of hepatotoxicity.

In light of the relatively high doses required to produce liver abnormalities in rats, the lack of clinically significant hepatic laboratory abnormalities in a database of >3,500 subjects and patients, and rates of hepatic abnormalities that are similar to patients treated with either placebo and oxycodone, there does not appear to be a hepatic safety signal for the proposed dosing regimen.

Cardiotoxicity

High doses of tapentadol produced inhibition in the hERG assay and QT prolongation was observed in *in vitro* and *in vivo* tests in the nonclinical program.

In the clinical development program, 12-lead ECGs were collected at specified visits and were analyzed at one of two centralized facilities,[ ]. The applicant used the EMEA criteria for clinically significant QT prolongation and subjected the ECG data to analyses to assess central tendencies and outliers or shifts from normal to abnormal. In comparing subjects and patients treated with tapentadol to placebo, no differences were observed. In addition, a thorough QT study was conducted (100 and 150 mg doses at steady-state). The QT study did not show QT prolongation. b(4)

In the context of the negative thorough QT study and the lack of signal in the clinical program, the QT prolongation observed in the nonclinical studies has been adequately addressed.

Abuse/Misuse/Addiction/Overdose

- The abuse liability study showed a liability similar to hydromorphone.
- In Study 34, a double-blind safety study, treatment was discontinued without a taper. For the patients treated with tapentadol, 7.6% to 17.3% of patients developed mild or moderate withdrawal signs and symptoms as assessed by COWS compared to 9.3% to 28.8% for patients treated with oxycodone. There was one serious adverse event coded as drug withdrawal syndrome.
- No overdoses were reported.

SAFETY CONCLUSIONS:

- Tapentadol has been studied in a sufficient number (>3,500) of subjects and patients for a sufficient duration (21% for >45 days) to support the proposed indication (acute pain).
- The adverse event profile appears typical for a mu opioid agonist with norepinephrine inhibition (tramadol being the prototype) with nausea, vomiting, dizziness, and somnolence being the most common adverse events.
- Given the observation of convulsions in dogs at clinically relevant doses and the fact that the applicant minimized the possibility of observing seizures in clinical trials through exclusion criteria, these facts should be conveyed in the labeling, at a minimum as a warning but possibly as a contraindication.
- Tapentadol has a significant abuse liability and the applicant's proposed Schedule II is appropriate.

9. Advisory Committee Meeting

No Advisory Committee Meeting is planned for this application.

10. Pediatrics

The applicant has requested a staged deferral request. I agree with the applicant's proposal.

11. Other Relevant Regulatory Issues

USE OF OXYCODONE AS A COMPARATOR:

The applicant has included oxycodone in three relevant Phase 3 studies: (Studies 32 and 33, efficacy studies in bunionectomy and end-stage osteoarthritis, respectively) and Protocol R33133-PAI-3004/KF5503/34 (Study 34) a randomized, double-blind, active-controlled 90-day safety study in patients with chronic low back pain or osteoarthritis.

[redacted] The other reference to oxycodone in the proposed labeling is in the common adverse event table. The applicant notes that the data are placebo- and oxycodone-controlled. However, the table does not show the incidences of common AEs for oxycodone.

b(4)

[redacted]

b(4)

b(4)

CLINICAL INVESTIGATOR NONCOMPLIANCE:

With regard to regulatory compliance, DSI conducted routine clinical investigator inspections and found irregularities at two sites. Dr. Norton found that the data from those sites were similar from the other sites.

12. Labeling

Labeling changes from the various disciplines have been recommended and are summarized here where possible. I agree with the proposed changes except as noted in *italics*. Final labeling is subject to review by upper management.

b(4)

b(4)

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Approval

- Risk Benefit Assessment

  Tapentadol is a New Molecular Entity that has been shown to be effective in replicated adequate and well-controlled clinical trials. The safety profile, based upon exposure to 3,515 humans, appears to be typical of a mu opioid agonist. The norepinephrine reuptake activity poses additional concerns for serotonin syndrome, QT prolongation, and, possibly, seizure, particularly in conjunction with drugs that affect CNS serotonin levels. Probably because the inclusion/exclusion criteria in the clinical trials addressed these risks, no peculiar toxicities were observed. The labeling should reflect the relatively restrictive patient population selected to mitigate the risk of these adverse events. If such labeling can be negotiated, the benefits appear to outweigh the risks for the proposed indication and dosing regimen. Dr. Fields has also recommended approval from the clinical perspective.

- Recommendation for Postmarketing Risk Management Activities

  At the current time, the Agency is not requiring special pharmacovigilance or risk management for immediate-release opioids.

- Recommendation for other Postmarketing Study Commitments

  The applicant must complete its pediatric program, as required by PREA. No other postmarketing requirements or commitments appear necessary at this time.

- Recommended Comments to Applicant

  Presuming that the label can be successfully negotiated, the only comment to the applicant is the reminder to complete the pediatric studies.

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/s/

Robert Shibuya
10/17/2008 09:52:19 AM
MEDICAL OFFICER