CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-304

OTHER REVIEW(S)

11/5/08

MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: November 4, 2008

To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)

Through: Michael Klein, Ph.D., Director
Silvia Calderon. Ph.D., Team Leader
Controlled Substance Staff (CSS)

From: Lori A. Love, M.D., Ph.D., Medical Officer
Controlled Substance Staff

Subject: Tapentadol HCl (NDA 22-304), immediate release
50 mg, 75 mg and 100 mg tablets
Indication: Relief of moderate to severe acute pain
Sponsor: Johnson & Johnson Pharmaceutical Research and Development, L.L.C. (J&JPRD)

At the request of DAARP, this memorandum provides expanded justification for CSS' recommendation to consider the possibility of requiring additional postmarketing requirements in addition to Controlled Substance Act (CSA) scheduling. The basis for the recommendation is to ensure that the benefits of tapentadol outweigh the-risks and include the requirement of a Medication Guide. CSS recognizes that tapentadol is being introduced as an immediate release formulation and that there is no precedent for the requirement of a Medication Guide for immediate release opioids. However tapentadol exhibits the following distinctive properties indicating a high potential for abuse:

1. Tapentadol is a new molecular entity analgesic that displays high affinity and selectivity for the μ opioid receptor, and additionally inhibits the reuptake of norepinephrine. It is an atypical μ opioid agonist in that does not structurally resemble other opioids such as morphine.

2. In a human abuse liability pharmacology study conducted by the Sponsor, tapentadol displays high abuse potential comparable to that of hydromorphone, a drug that is associated with high levels of abuse. In this study single doses of tapentadol (50, 100, and 200 mg) had a similar abuse liability profile of subjective effects to that of calculated equianalgesic single doses of 4 mg, 8 mg, and 16 mg of hydromorphone, respectively.

3. Based on the human abuse liability study and from the point of view of the potential for abuse, 50 mg of tapentadol (lowest tablet strength to be marketed) produces comparable opioid effects (liking, euphoria, etc) to that of 4 mg of hydromorphone.

4. The CSA imposes tight controls in the manufacturing, importation/exportation, distribution and prescription of Schedule II opioids, leaving patients outside the regulatory loop created by the Act. Thus, to avoid high levels of misuse and abuse of tapentadol, which might counterbalance the beneficial therapeutic properties of the drug, it is recommended that physicians and patients receive training and education in the use of the drug product from the time it is introduced on the market.

5. CSS recognizes that there are few mechanisms to reach and educate health care professionals that will prescribe tapentadol tablets, as well as for patients and family members on the appropriate use of this novel analgesic. CSS suggests that a medication guide that emphasizes the following may be appropriate for tapentadol IR:

    - Tapentadol is a μ opioid agonist with effects and adverse events, including addiction and abuse, similar to other strong opioids, such as hydromorphone and oxycodone. This point needs to be emphasized in the product labeling.
    - Tapentadol IR is only approved for acute usage, and should not be used chronically as this increases the adverse event profile, including the likelihood for addiction and abuse.
    - Specific instructions on appropriate patient selection and drug dosing should be provided such as [don't take more than directed, what to do in case of a missed dose, don't share drug, how to safely store the drug, etc,].

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MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date:	October 17, 2008
To:	Bob Rappaport, M.D., Director Division of Anesthesia, Analgesia, and Rheumatology Products
Through:	Michael Klein, Ph.D., Director Controlled Substance Staff
From:	Lori A. Love, M.D., Ph.D., Medical Officer Controlled Substance Staff (CSS)
Subject:	Tapentadol HCl (NDA 22-304), immediate release 50 mg, 75 mg and 100 mg tablets Indication: Relief of moderate to severe acute pain **Sponsor:** Johnson & Johnson Pharmaceutical Research and Development, L.L.C. (J&JPRD)
Materials received:	NDA 22-304 is located in the EDR.

Submission:
This review provides recommendations to the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) regarding the abuse potential of tapentadol[1].

I. Background

Tapentadol is a new molecular entity with CNS analgesic properties. It has both μ opioid agonist receptor agonist properties and inhibits the reuptake of norepinephrine (NE). Both properties are relevant for the management of pain. Tapentadol 50 mg, 75 mg and 100 mg tablets is indicated for the relief of moderate to severe acute pain.

In clinical studies tapentadol showed comparable potency to other Schedule II narcotics such as morphine and oxycodone, and showed a similar abuse potential profile of subjective effects to that of calculated equianalgesic doses of hydromorphone. The sponsor in their scheduling

[1] Information for this review was also taken from: E. Fields, DFS Clinical Review NDA 22-304, 09/18/2008 and D. Lee, DFS Clinical Pharmacology Review NDA 22-304, 9/30/08.

information requested that tapentadol be scheduled under Schedule II of the Controlled Substance Act (CSA).

II. Conclusions and Recommendations

- Receptor binding studies show that tapentadol displays high affinity and selectivity for μ opioid receptors and inhibits the reuptake of NE. Drugs that bind to the μ opioid receptors with high affinity have abuse potential and include such Schedule II drugs as morphine, oxycodone and hydromorphone.
- Tapentadol, like morphine, has rewarding effects in rats and acts as a positive reinforcer in monkeys.
- Tapentadol has the potential to induce physical dependence of the opioid type as demonstrated in animal studies of withdrawal and in the clinical setting.
- In a clinical abuse potential study conducted in subjects with a prior history of opioid abuse, single doses of 50 mg, 100 mg and 200 mg of tapentadol had a similar abuse potential profile of subjective effects to that of single doses of 4 mg, 8 mg and 16 mg of hydromorphone respectively. Thus, a 50 mg dose of tapentadol, which represents the lowest available dosage strength, will produce similar euphorigenic and subjective effects to that of 4 mg of hydromorphone, a dose currently associated with high levels of abuse.
- CSS concurred with the Sponsor's proposal for control of tapentadol in Schedule II of the CSA and consequently initiated the procedure to finalize this action.
- Although tapentadol will be subject to Schedule II controls as is hydromorphone, the risks of abuse and misuse of tapentadol is high and might require additional postmarketing efforts that go beyond scheduling controls to maintain a positive benefit-risk assessment.

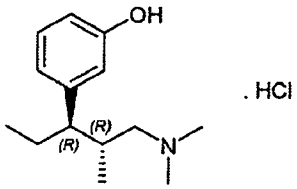
III. Summary

A. Clinical Studies

Thirty-one clinical trials were completed during the development of tapentadol immediate release (IR) formulation (20 Phase 1, and 11 Phase 2/3 double-blind studies). The efficacy and safety of tapentadol in the treatment of moderate to severe acute pain was established in two randomized, double-blind, placebo- and active-controlled (Oxycodone) studies of moderate to severe pain from first metatarsal bunionectomy (Study KF5503/32) and end-stage degenerative joint disease (Study KF5503/33), using tapentadol in doses of 50 mg, 75 mg, and 100 mg every 4 to 6 hours.

B. Chemistry and Pharmacology

Tapentadol HCl tablets are immediate-release film-coated tablets. The chemical name is 3-[(1R,2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol monohydrochloride. The structural formula is:



The pKa values are 9.34 and 10.45.

- Pharmacodynamics

Tapentadol is 18-times less potent than morphine in binding to the human μ opioid receptor and is 2-3 times less potent in producing analgesia in animal models, consistent with its dual mode of action. Unlike morphine, tapentadol also inhibits norepinephrine reuptake resulting in increased norepinephrine concentrations. Tapentadol exerts its pharmacodynamic effects directly without a pharmacologically active metabolite.

- Pharmacokinetics

Tapentadol is rapidly and completely absorbed after oral administration. Mean absolute bioavailability after single-dose administration (fasting) is approximately 32% due to extensive first-pass metabolism. Maximum serum concentrations of tapentadol are typically observed at around 1.25 hours after dosing. The terminal half-life is on average 4 hours after oral administration. The total clearance is 1530 +/- 177 ml/min.

Dose-proportional increases in the Cmax and AUC values of tapentadol have been observed over the oral therapeutic dose range. A multiple (every 6 hour) dose study with doses ranging from 75 to 175 mg tapentadol showed a mean accumulation factor of 1.6 for the parent drug and 1.8 for the major metabolite tapentadol-O-glucuronide, which are primarily determined by the dosing interval and apparent half-life of tapentadol and its metabolites.

- Metabolism and elimination

About 97% of the parent compound is metabolized, primarily via conjugation with glucuronic acid to produce glucuronides. Following oral administration approximately 70% (55% glucuronide and 15% sulfate of tapentadol of the dose is excreted in urine in the conjugated form, and 3% of drug was excreted unchanged. Tapentadol is additionally metabolized to N-desmethyl tapentadol (13%) by CYP2C9 and CYP2C19 to hydroxytapentadol (2%) by CYP2D6, which are further metabolized by conjugation. None of the metabolites contributes to the analgesic activity. Tapentadol and its metabolites are excreted almost exclusively (99%) via the kidneys.

C. Abuse Potential

- Receptor Binding Studies

Receptor binding studies show that tapentadol has higher affinity for μ opioid receptors than for κ and δ receptors. Tapentadol binds to μ opioid receptors labeled with naloxone with a Ki of 96 nM, showing less affinity for δ receptors labeled with the ligand DPDPE (Ki= 970 nM) and for κ receptors labeled with the selective ligand CI-977 (Ki= 910 nM). In receptor binding studies on

cloned human μ opioid receptors labeled with titrated naloxone, tapentadol showed high affinity with a Ki of 60 nM, whereas its major metabolite, the phenolic O-glucuronide derivative showed no relevant binding affinity at the human μ opioid receptor up to a concentration of 10 μM

Tapentadol showed strong agonist activity comparable to that of morphine in stimulating μ opioid receptor-mediated G-protein activation using agonist-stimulated [^{35}S]GTPγS binding in cells expressing the cloned human μ receptors.

In addition to its opioid activity, tapentadol inhibits the reuptake of NE with a Ki of 480 nM and has weak inhibitory activity on the 5-HT uptake of rat brain synaptosomes. The *in vivo* relevance of the effects of tapentadol on NE and 5-HT transporter systems was evaluated in a microdialysis study in rats. Tapentadol elicited a dose-dependent increase of extracellular levels of NE in the ventral hippocampus (up to approx. 450% above baseline) and, to a much lesser extent, of 5-HT (approx. 130% above baseline). Morphine did not increase NE concentrations but tended to increase 5-HT concentrations.

- Subjective Effects, Drug Discrimination Studies

Tapentadol in doses of 1-10 mg ip in rats showed a dose-dependent, full generalization to the morphine (3.16 mg/kg) training cue, but did not produce an amphetamine-appropriate response. Morphine also showed a dose-dependent, full generalization to the morphine cue. The potency for generalization to a morphine cue was 2.4 times lower than the potency of morphine itself. These ratios are roughly equal to the potency differences in rat pain models and also to the relative potencies of these compounds in conditioned place preference studies.

- Rewarding and Reinforcing Effects

The rewarding effects of tapentadol were evaluated in the conditioned place preference paradigm in rats. Tapentadol and morphine produced a conditioned place preference at doses of 2.15 mg/kg and 1.47 mg/kg, respectively. These results indicate that both morphine and tapentadol have rewarding effects. These positive preferences were antagonized by naloxone, indicating that the rewarding effects of these drugs mainly relate to their μ opioid receptor activity. No locomotor sensitization was seen with any dose of tapentadol during the conditioning experiment.

Tapentadol's reinforcing properties were investigated in intravenous self-administration experiments in Rhesus monkeys, trained to self-administer morphine sulfate (0.03 mg/kg/infusion). Tapentadol in the dose range of 0.01 to 0.3 mg/kg/infusion dose-dependently maintained self-administration behavior in morphine sulfate experienced monkeys.

- Clinical Abuse Liability Studies

The abuse potential of tapentadol (50 mg, 100 mg and 200 mg) was assessed relative to the Schedule II opioid, hydromorphone (4 mg, 8 mg and 16 mg) in 40 opioid-experienced, non-dependent subjects. The study design was an equianalgesic single-dose, double-blind, double-dummy, placebo-controlled, randomized, crossover (Study HP5503/14). The highest recommended therapeutic dose is 100 mg every 4 to 6 hours. Thus, the highest dose of tapentadol tested in the abuse liability study was twice the recommended therapeutic dose.

Several assessments and scales[2] were used in the study to assess the positive and negative subjective drug effects produced by tapentadol and the Schedule II active comparator. Additional tests were used to evaluate the sedative, stimulant and the effects of tapentadol in comparison to hydromorphone and placebo on cognitive performance.

The mean peak Overall Drug Liking scores over 24 hours postdose, the primary pharmacodynamic endpoint of the study, for all the tapentadol doses were significantly different from placebo. Based on responses on a 100 mm VAS, the mean peak Overall Drug Liking scores increased in a dose-related manner after administration of tapentadol (from 59.1 mm to 73.0 mm) and the opioid hydromorphone (from 60.6 mm to 71.4 mm); after placebo, the mean peak score was 48.8 mm. Statistically significant differences were demonstrated between each tapentadol or hydromorphone dose and placebo and a similar dose-response relationship was observed between tapentadol and hydromorphone.

The mean positive subjective effects for tapentadol and hydromorphone (Schedule II) tended to reach the highest values at one to two hours postdose. Both drugs decreased visual-motor coordination at the higher doses tested.

- Dependence and Withdrawal

The potential of tapentadol to produce physical dependence was examined in animal models and in the clinical trials setting. In the acute mouse model, withdrawal was precipitated by a high dose of naloxone after two day pretreatment with increasing doses of tapentadol or morphine. In the chronic rat model, animals were pretreated for several weeks with either tapentadol or morphine, and withdrawal was induced by naloxone challenge (precipitated withdrawal) or by cessation of drug treatment (spontaneous withdrawal). In all animal experiments, the animals treated with tapentadol showed signs of physical withdrawal. However, tapentadol produced fewer withdrawal symptoms than equianalgesic doses of morphine.

Withdrawal was specifically evaluated in clinical study KF5503/34, a safety study where tapentadol was administered as flexible doses of 50 mg or 100 mg every 4 to 6 hours, as needed, over a 90 day period in subjects with low back pain or pain from knee or hip osteoarthritis. Assessment consisted of evaluation of treatment emergent adverse events of withdrawal during the trial, as a more formal assessment at the end of the study where tapentadol was withdrawn without taper. Subjects were evaluated using the Clinical Opiate Withdrawal Scale [COWS] and Subjective Opiate Withdrawal Scale [SOWS]) at the follow-up visit.

Subjects taking tapentadol appeared less likely to have withdrawal symptoms assessed with COWS than subjects with oxycodone (17% versus 29%). No difference in withdrawal symptom severity was noted between the tapentadol and oxycodone groups, as assessed with SOWS total score.

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[2] Overall Drug Liking, Subject-Rated Opiate Agonist Scale, Addiction Center Inventory, Cole Version (Cole/ARCI), Subjective Effects Visual Analogue Scales (VAS), Subjective Drug Value, Observer-Rated Single-Dose Questionnaire, Divided Attention Test and Choice Reaction Time Test. The Cole ARCI includes Sedation, Unpleasantness-Dysphoria, Stimulation-Euphoria and Abuse Potential Subscales and the VAS include "Any Drug Effect", "Good Drug Effects"," Bad Drug Effects", "High", "Take the Drug Again" and "Drug Liking" measures.

Nine subjects (1%) in the tapentadol group and 2 subjects (1%) in the oxycodone group reported drug withdrawal syndrome. Of these, a single case of withdrawal symptoms (elevated systolic blood pressure, irritability, and anxiety) was listed as a serious adverse event for a subject who had received treatment with tapentadol (250 mg to 600 mg total daily dose) for 94 days. Drug withdrawal syndrome was not reported in any other efficacy clinical trial.

D. Clinical Safety

- Adverse Events

During clinical development, there were no deaths attributable to tapentadol IR. The adverse events reported were similar to those found with other related opioid analgesics. The most common adverse reactions (reported by ≥10% in any tapentadol dose group) were nausea, dizziness, vomiting, somnolence, and headache. The incidence of vomiting, nausea and dizziness was noted to be lower for tapentadol than for hydromorphone. Euphoric mood, disorientation, confusional state, restlessness, hallucinations, agitation, nervousness, thinking abnormal, disturbance in attention, paraesthesia, sedation, depressed level of consciousness, memory impairment, ataxia and coordination abnormal, dyspnea, respiratory depression and decreased blood pressure were reported in less than one percent of tapentadol treated subjects.

- Overdose

No case of overdose was reported in the completed studies with tapentadol IR. One subject who received tapentadol ER in an ongoing 1-year, open-label, Phase 3 clinical study (KF5503/24) reported an overdosage with euphoria and visual disturbance.

- Drug Accountability and Diversion

Drug accountability and compliance with study drug treatment was assessed for the 3 longer-term Phase 3 clinical studies (KF5503/33 [10 days], KF5503/34 [90 days], and the open-label extension period in KF5503/32 [9 days]. A small number of patients self-administered more than the intended daily dose of tapentadol IR, up to 1200mg/day for one or two days. All subjects had prior opioid experience and none reported an adverse event. In study KF5503/34, fewer subjects in the tapentadol IR group (9%) than in the oxycodone IR group (12%) took more than 14 capsules on any day for 1 or more days.

There were no reports of study drug diversion.

- Postmarketing Risk Management

The sponsor identified important and potential risks associated with tapentadol IR in Table 1, and proposed routine and product specific pharmacovigilance to address these concerns.

Table 1: Summary of Safety Concerns

Safety Concerns
Important identified risks:
Potential for abuse
Seizure
Important potential risks:
Overdose
Off-label use, incl. pediatric patients
Potential for medication errors (inappropriate prescribing, inappropriate dosing, inappropriate use) and patient misuse
Accidental exposure
Diversion
Important missing information:
Use in pediatrics

Source: Tapentadol IR Safety Surveillance Plan

From the data obtained during clinical development, the risks for abuse, misuse and diversion of tapentadol IR are likely to be extremely high, and safe use of this product will be contingent on effective management of these risks postmarketing. Although the agency has not as yet required a Risk Evaluation and Mitigation Strategy (REMS) for immediate release opioid products, consideration of a REMS may be appropriate for this product.

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