Summary of Safety Results and Conclusions

Exposure

A total of 3515 subjects were exposed to at least one dose of tapentadol IR during the development program, 467 during Phase 1 trials, 870 in Phase 2 single-dose trials, and 2178 in nine Phase 2/3 multiple-dose, double-blind trials. Phase 2/3 multiple-dose double-blind trials were carried out in the following populations: post-operative dental pain, post-operative bunionectomy pain, chronic non-malignant pain, end-stage joint disease, osteoarthritis, and chronic low back pain.

In the Phase 2/3 multiple-dose, double-blind trials, 2,034 subjects received 50mg-100mg per dose. A total of 449 subjects received flexible dosing of 50mg or 100mg every 4-6 hours as needed for at least 45 days, and 318 of these subjects received tapentadol IR for at least 90 days.

Therefore, in regard to the sought indication, an adequate number of subjects have been exposed to tapentadol IR to meet the ICH guidelines for exposure.

Deaths and Serious Adverse Events (SAEs)

No deaths were reported after treatment with tapentadol IR in any of the completed Phase 1 through 3 studies. Four deaths were reported in the Phase 3 tapentadol ER ongoing studies as of March 15, 2008. Details are located in Section 7.3.1.

There were a total of 21 nonfatal SAEs reported in 17 subjects from all phases of the completed studies in the tapentadol IR development program in subjects who received tapentadol IR. Serious adverse events occurred in 1% of subjects in the multiple-dose, double-blind safety analysis set treated with either tapentadol IR or oxycodone. The rate of SAEs in placebo treated patients was <1%.

The most commonly occurring SAEs (by System Organ Class (SOC) included cardiac disorders and nervous system disorders. All SOCs or individual preferred terms occurred in <1% of treated subjects in the tapentadol IR group. The occurrence of SAEs did not appear to be dose related. Details regarding all SAEs are located in Section 7.3.2.

Common Adverse Events

Treatment emergent adverse events (TEAEs) occurred in 76% of the "all" tapentadol group in the multiple-dose, double-blind safety analysis set, compared to 47% in the placebo group and 84% in the "all" oxycodone group. The most common TEAEs in the tapentadol IR group were nausea, dizziness, vomiting, somnolence, headache, constipation and pruritis. These occurred at a greater rate in the tapentadol IR group than in the placebo group. TEAEs related to asthenic conditions when combined (fatigue, lethargy, asthenia and malaise) were also common. The incidence of TEAEs appeared to be dose related.

There were no meaningful differences in adverse events reported with respect to age or racial groups. There was, however, an observation of a higher incidence of nausea, vomiting and dizziness in women compared to men treated with tapentadol IR or oxycodone IR compared to placebo.

A full discussion of TEAEs may be found in Section 7.4.1.

Adverse Events of Interest

The Division requested that SMQs be performed on the pooled TEAE data for 1) severe cutaneous reactions and 2) possible drug-related hepatic disorders. In the nine Phase 2/3 multiple-dose, double-blind studies, the percentage of subjects with TEAEs included in the severe cutaneous reactions SMQ was <1% in the "all" tapentadol group, similar to the percentage in the placebo group (<1%). The data do not point to a signal regarding severe cutaneous reactions of tapentadol IR.

The percentage of subjects with adverse events included in the possible drug-related hepatic disorders SMQ was 1% in both the "all" tapentadol group and the placebo group. The most commonly reported events in the "all" tapentadol group included increased GGT (<1%), ALT (<1%), and AST (<1%). In evaluation of laboratory abnormalities, no treatment-related laboratory findings were evident for liver function tests. Details of the SMQ analyses are located in Section 7.5.5, and laboratory evaluations in Section 7.4.2.

There was one report of seizure in the Phase 1 trial HF5503/10. This subject had a history of seizures ("grand-mal epilepsy) which was withheld during screening. He had stopped taking his seizure medication (valproic acid) a few months prior to enrollment in the study.

Laboratory Tests and Vital Signs

The only laboratory test result or vital sign measurement that showed consistent patterns that would indicate a potential for clinically relevant safety concerns in the Phase 1, 2, or 3 completed studies of tapentadol IR was oxygen saturation as measured by pulse oximetry. No consistent changes in cardiac parameters of heart rate or blood pressure were observed. In studies that measured oxygen saturation by pulse oximetry, a dose-dependent increase in the number of subjects with oxygen desaturation was detected with tapentadol IR. Similar findings were observed in with oxycodone IR; these findings reflect the mu-opioid agonist properties of tapentadol IR. Laboratory evaluations and vital signs are discussed in Sections 7.4.2 and 7.4.3 respectively.

ECG/QT Interval

In a thorough QT Phase 1 study, no effect of therapeutic (100 mg) and supratherapeutic (150 mg) doses of tapentadol IR on the QT interval was shown. Similarly, tapentadol IR had no relevant effect on other ECG parameters of heart rate, PR interval, QRS duration, T-wave or U-wave morphology. The assay sensitivity of the study was validated by the expected QTc prolongation observed in the moxifloxacin group.

There was no evidence of drug-related ECG abnormalities in the analysis of ECGs obtained during the Phase 1, 2, or 3 studies of tapentadol IR.

Evaluation of ECGs and the TQT study are discussed in Sections 7.4.4 and 7.4.5 respectively.

Drug-Disease Interactions

The results of the Phase 1 drug-disease interaction studies in subjects with hepatic impairment (HP5503/16) and in subjects with renal impairment (HP5503/15) demonstrated that, although there were effects on the pharmacokinetics of the parent compound or of the major metabolite, tapentadol IR was well tolerated with a safety profile similar to that observed in other single-dose tapentadol IR studies in healthy subjects. Nevertheless, the Applicant's dosing recommendations will reflect the results of the pharmacokinetic assessment in these populations, considering the potential outcomes in multiple-dosing situations

These studies are discussed in Section 7.5.3

Drug-drug interactions

No clinically relevant interactions were observed in the 4 Phase 1 drug-drug interaction studies when tapentadol IR was coadministered with metoclopramide (HP5503/19), probenecid (HP5503/21), naproxen and ASA (HP5503/22), or acetaminophen (HP5503/23). There was however approximately twice the percentage of reports of vomiting and somnolence in the group that received omeprazole plus tapentadol compared to tapentadol alone in Study (HP5503/20). There were not however changes in the PK parameters of tapentadol when coadministered with omeprazole.

These studies are discussed in Section 7.5.4.

Abuse liability, overdose, and withdrawal

Results from a Phase 1 study, conducted in opiate-experienced, nondependent subjects, showed that single doses of tapentadol IR (50, 100, and 200 mg) had a similar abuse liability profile to that of hydromorphone IR (4, 8, and 16 mg).

No cases of overdose were reported in the completed studies with tapentadol IR.

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.

Withdrawal was evaluated in one study (KF5503/34). Seventeen percent of subjects in the tapentadol treatment group reported at least one withdrawal symptom. One percent (9/679) of subjects experienced drug withdrawal syndrome, one of which was coded as a serious adverse event (elevated systolic BP, irritability and anxiety).

It is clear that withdrawal can occur following abrupt cessation of tapentadol IR administration.

There were no reports of study drug diversion.

Abuse liability, overdose, and withdrawal are discussed in detail in Section 7.6.3.

Comparison with oxycodone

Throughout the Phase 2/3 multiple-dose double-blind studies, oxycodone was used as an active comparator to assess assay sensitivity. Safety data was collected on all subjects in the oxycodone treatment groups, and the rates of adverse events for tapentadol IR were compared to both placebo and oxycodone. The incidence of gastrointestinal events (nausea, vomiting, and constipation) was lower in the "all" tapentadol group compared to the "all" oxycodone group. The overall incidence of CNS effects of somnolence and dizziness was similar for tapentadol IR and oxycodone treated subjects, however in study KF5503/32 (post-operative bunionectomy pain), the incidence of somnolence was reported approximately twice as frequently in the tapentadol IR 100mg group (21%) than in the oxycodone 15mg IR group (10%).

The findings in the 2 pivotal Phase 3 studies are supported by the results of the Phase 3, 90-day safety study. In this study, comparisons between tapentadol IR (flexible doses of 50 mg or 100 mg) and oxycodone HCl IR (flexible doses of 10 mg or 15 mg) showed a lower likelihood of nausea, vomiting, nausea/vomiting (the composite nausea or vomiting), and constipation with tapentadol IR vs. oxycodone IR, and a similar likelihood of somnolence or dizziness between the tapentadol IR and oxycodone IR treatments.

Pertinent negatives

There were no reports of seizures during the development of tapentadol IR. This is relevant because of the known risk of seizures associated with Tramadol, and the similarity in the mechanisms of action of the two drugs.

Given that tapentadol is structurally related to tramadol whose labeling contains language warning about the risks of serotonin syndrome and tapentadol's selective norepinephrine reuptake inhibitor activity, tapentadol carries at least a theoretical risk of precipitating serotonin syndrome. Therefore, the following analysis was performed by Dr. Robert Shibuya.

The integrated database for the Phase 2/3 studies, excluding periods when subjects were not on study drug (screening, post-treatment), was searched for the following verbatim terms: serotonin, syndrome, myoclonus, tremor, fever, tachycardia, diaphoresis, mydriasis, hyperreflexia, hyperthermia, pyrexia, clonus, and hypertension. Patients treated with morphine or ibuprofen were also excluded due to small numbers. One hundred and four adverse events, occurring in 101 subjects were identified. These are summarized in Table 32b, below.

Table 32b: Adverse events associated with serotonin syndrome (tapentadol, placebo, and oxycodone-treated subjects only)

Sx/Si	Severity	Tapentadol	Placebo	Oxycodone
n (%)		2178	619	675
Diaphoresis	Total	41 (1.9)	1 (0.3)	11 (1.6)
	Mild	23	1	6
	Moderate	16		5
	Severe	2	1	
Fever	Total	14 (0.6)	0	3 (0.4)
	Mild	12		2
	Moderate	2		1
HTN	Total	16 (0.7)	2 (0.3)	0
	Mild	13	2	
	Moderate	3		
Tachycardia	Total	14 (0.6)	1 (0.3)	0
	Mild	8	1	
	Moderate	5		
	Severe	1		

Table 32b shows that the non-specific symptoms and signs associated with serotonin syndrome were observed more frequently in subjects treated with tapentadol than with the comparators. However, it should be noted that serotonin syndrome is a constellation of symptoms and signs. Three subjects experienced more than one adverse event associated with serotonin syndrome. Details are summarized in Table 32c.

Table 32c: Adverse events associated with serotonin syndrome reported more than once in a subject

Subject ID	Treatment	AE	Severity*	Related*
KF5504/04-005-5180	Tapentadol	HTN	Mild	No
KF5504/04-005-5180	Tapentadol	HTN	Mild	No
KF5504/04-005-5232	Placebo	Tachycardia	Mild	Possible
KF5504/04-005-5232	Placebo	Diaphoresis	Mild	Unlikely
KF5503/22-006-600001	Tapentadol	Diaphoresis	Mild	Probable
KF5503/22-006-600001	Tapentadol	Diaphoresis	Mild	Possible

*Severity and relationship to study drug administration were both in the investigator's judgment

Table 32c shows that three subjects experienced more than one serotonin syndrome-related adverse event. However, each subject only experienced two AEs and one of the subjects was treated with placebo. Therefore, it is extremely unlikely that any of these cases represented serotonin syndrome.

Overall, there was no evidence that tapentadol resulted in serotonin syndrome.

Overall conclusions

The safety profile of tapentadol IR was demonstrated in over 3500 subjects treated with tapentadol IR in the completed Phase 1, 2, and 3 studies. Tapentadol IR appears reasonably well tolerated across the intended marketed dose range (50mg, 75mg, or 100mg every 4 to 6 hours as needed) in both inpatient and outpatient settings. The profile

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.