toxicity was reversible at the doses, routes and durations studied, based on absence of hepatotoxic findings after treatment-free recovery periods.

Dog:

Repeated dose toxicology studies were conducted in Beagle dogs, with dosing durations of 10 and 28 days by the IV route, 9 days and 13-weeks by the SC route, and 2, 13, and 52 weeks by oral gavage. The main target organs of toxicity in the dog were the CNS, and gastrointestinal (GI) and cardiovascular (CV) systems.

Intravenous toxicity was assessed in M and F dogs given tapentadol for up to 10 consecutive days (1-7.5 mg/kg/day for 4 consecutive days with sacrifice 12 days after the last dose in the first dose-escalation phase dogs, and 7.5 mg/kg/day for 10 consecutive days with sacrifice 24 hours after the last dose in the maintenance treatment (second study phase) dogs. The results showed transient, treatment-related salivation (M), restlessness and whimpering (F, ≥5 mg/kg/day), and rhinorrhea, panting, labored breathing, decreased activity and uncoordinated movements at 7.5 mg/kg/day, with lateral recumbency in the HD M and limb buckling in the HD F. The clinical signs were evident during or immediately after injection, and lasted approximately 1-3 hours after the injections. There were slight decreases in food consumption in the M and F at ≥5 mg/kg/day, and slight body weight loss in the HDF after treatment Day 2. Moderate body weight loss was found in most HD animals at the end of the 10-day treatment period. There were observations at the HD of increased glutamate dehydrogenase, total lipids, cholesterol, triglyceride, phospholipid, iron concentration and protein at the end of the study. Histopathology was not conducted in this study, but the macroscopic examination showed red foci at the injection sites in HD dogs.

A subsequent 4-week study on intravenous tapentadol toxicity in dogs (1-7.5 mg/kg/day) showed treatment-related clinical signs consistent with those observed in the 10-day study, with dose-related increases in incidence and severity of excessive salivation, decreased activity, hind-leg buckling uncoordinated movements, vomiting, urination, ventral recumbency and rhinorrhea beginning during or immediately after injection and lasting for 1-2 hours. Tachypnea, panting, retching, and defecation were seen with less frequency than were the other signs. Food consumption (F at ≥3 mg/kg/day and HD M) and body weights (HD F) were reduced in the F (≥3 mg/kg/day). There were no treatment-related effects on any other parameter, including ophthalmologic examinations, electrocardiograms (including QT interval), and inspection of the injection sites. Special assessments of microsomal drug metabolizing enzymes in the livers at necroscopy showed no inhibition or induction of P450 enzymes, and no effects on phase II aminophenol glucuronyl transferase activity.

Subcutaneous tapentadol toxicity was tested in Beagle dogs dosed for a 7-9-day period (10 mg/kg b.i.d. followed by 7.5 mg/kg b.i.d.). The treatment-related findings were similar to those in the IV toxicology studies in dogs, and included CNS behavioral signs

known to be associated with opioid receptor agonist activity. The observations were dose-related increases in incidence and severity of decreased activity, recumbency, tremor, salivation, somnolence, forelimb and hindlimb buckling, uncoordinated movements and occasional whimpering. The male dogs also showed vomiting, and occasional pale or loose feces and fecal mucus. Several dogs showed injection site swelling. Food intake and body weights were reduced in the first dosing week in both treatment periods, and resolved after increasing the duration of the feeding period over the remainder of the study period. The reversibility of reduced food consumption and body weights, and observed decreases in the severity of the behavioral effects may have also been related to development of partial tolerance to tapentadol effects.

Two 3-month SC tapentadol toxicity studies were conducted in Beagle dogs (20-160 mg/kg/day dose escalation phase for 13 days followed by 40 mg/kg/day treatment phase on Days 14-91 in the first study, and 4-16 mg/kg/day in the second study). One F dog given 16 mg/kg/day died on dosing day 17 in the second study. The treatment-related clinical signs were similar to those observed in the IV toxicity studies in dogs, and included dose related restlessness, decreased activity, drowsiness, fearfulness, vocalization, unsteady gait, hindlimb weakness, ventral recumbency, spontaneous urination and defecation, vomiting and salivation, with increased respiratory frequency and forced respiration in several animals beginning around 30 minutes after dosing and lasting for up to 5 hours. The higher doses administered (≥40 mg/kg/day SC) produced defense behavior, tremor, twitches, and convulsions in 1 dog. A potential relationship of the tremors to possible seizure activity was not addressed. Acute tolerance was suggested by observed decreases in severity and duration of the behavioral signs after the second than after the first daily doses. Also, the clinical signs were progressively reduced in severity over the course of the treatment duration, further suggesting the development of partial tolerance to tapentadol CNS effects. Injection site inspections indicated that the dogs scratched the sites throughout the study. Reduced body weights, body temperature and heart rate observed early in the studies showed gradual, slight recovery throughout the dosing periods, but body weights remained below control levels at the end of the second study. Food consumption, greatly reduced during the first weeks of treatment, was also only partially reversed by extension of the feeding periods. The results of the ECG measurements showed treatment-related absolute and corrected QT prolongation at 30 minutes after dosing compared to baseline values in the dogs given ≥4 mg/kg b.i.d during Week 1, and trends toward increased absolute QT values in Weeks 4 and 13.

The necroscopic examination in the 3-month SC toxicity studies in dogs showed local toxicity at the injection sites in both studies. The main injection site findings were subcutaneous ecchymoses with hemorrhages, edema and gelatinous consistency of underlying tissues, that indicated scratching by the dogs throughout the first study. There was considerable local injection site toxicity in the second study that was qualitatively similar to the findings in the first SC study, with dark red discoloration, hemorrhages, acute and subacute inflammatory infiltrates, fibrosis, phlebitis and thrombophlebitis, and at the HD (16 mg/kg/day) chronic focal or multifocal perivasculitis. The injection site effects were only partially reversible during the 4-week

recovery period, and suggested that the SC route is likely not suitable for evaluation of chronic tapentadol toxicity in dogs. Tapentadol-related GI toxicity was evident in the necropsy in the second study, by findings of hemorrhage in the mesentery, and dark red discolorations in the stomach, and small and large intestines. Toxicokinetic analyses showed consistent exposure to the test article and the metabolite tapentadol-O-glucuronide, with dose-proportional increases in concentrations, peak plasma concentrations at approximately 0.5 h, and considerably higher exposure to the metabolite ($t_{1/2}$ = 4h) than to the parent drug ($t_{1/2}$ = 1.77 h). Parent drug exposure (AUC) was higher in the dog that convulsed than in the other dogs, but there were no differences in peak plasma tapentadol concentration (Cmax).

Oral (gavage) tapentadol toxicity was tested in two 2-week, and in 13- and 52-week studies in dog. The 2-week studies evaluated doses of 50 and 150 mg/kg/day in the first, and in the second study there was a 13-day dose escalation period (10-350 mg/kg/day) followed by a dose de-escalation period from 320 down to 200 mg/kg/day for 14 days. The clinical signs of tapentadol toxicity were generally similar to those observed in the IV and SC assays in the dogs (salivation, vomiting, irregular respiration, and recumbency), with observations of whimpering (≥220 mg/kg/day), somnolence (≥280 mg/kg/day), dyspnea , tachypnea or panting (≥80 mg/kg/day) and tremors (≥160 mg/kg/day) beginning approximately 15 minutes after oral dosing and persisting for up to 8 hours at the higher doses in the second assay. Convulsions were observed in several dogs in the first (1 M and 1 F at 50 mg/kg/day, and 1 M and 1 F at 150 mg/kg/day) and second (1F at 350, 320, 280, and occasionally at 200 mg/kg/day) study. ECG and hearing measurements were normal in both studies. Liver weights were increased in all treated dogs in the second but not in the first study, in the dogs given the dose escalations up to 350 mg/kg/day and then de-escalation from 350 to 200 mg/kg/day. Observed treatment-related increases in liver weights were without clinical laboratory, and macroscopic and microscopic correlates. Treatment-related GI toxicity revealed in the necropsies was manifest by activation of the enteric lymphatic system (Peyer's patches) in the small and large intestines with activated lymphoid follicles in the gastric mucosa and proximal small intestine suggesting hyperplasia in the germinal centers characteristic of gastrointestinal immune response.

The results of 13-week oral tapentadol toxicity observations in Beagle dogs (10-80 mg/kg/day) were comparable to those in the shorter term (2-week) oral studies and to the toxicity found by the IV and SC routes. Initial HD administration at 120 mg/kg/day produced severe CNS toxicity, beginning 15-30 minutes after dosing and lasting for up to 5 hours. The signs included tachypnea, apathy and convulsions with paddling movements, twitching and tremors, and mortality in 2 M dogs, prompting lowering the dose to 80 mg/kg/day on treatment Day 23 until the end of the study. The convulsions were observed at 30-60 minutes after tapentadol administration, except for a convulsion immediately after dosing in one of the F. Food consumption was reduced in the M (HD) and F (≥35 mg/kg/day), predominantly during the first several weeks of dosing. Body weight gain was reduced at the HD. The treatment-related effects on clinical signs and body weights were reversible after the 4-week recovery period.

ECG assessments in the 13-week oral toxicity study in dogs showed QT prolongation, with similar results after correction for heart rate (QTc), at 35 mg/kg/day in Week 13, and in the high-dose groups in Weeks 1 (120 mg/kg/day) and 13 (80 mg/kg/day). Treatment-related decreased gamma glutamyltransferase and increased serum sodium were found. Macroscopic and microscopic examinations during necropsy showed thymic atrophy and prostate gland inflammation (≥35 mg/kg/day) and adrenal cortical hypertrophy in the M ≥35 mg/kg/day). Hepatic microsomal enzyme activity analysis in liver samples recovered during the necropsy in the HD and control dogs showed a statistically significant treatment-related induction of aminopyrine N-demethylase activity in the M and F, and inhibition of glucuronyltransferase activity in the M. The NOAEL in this study (10 mg/kg/day) represented systemic exposure to the parent drug of approximately 0.04 times the clinical exposure at the MRHD of 600 mg/kg/day on an AUC basis, and on a Cmax basis, relevant to the CNS and cardiovascular effects noted during the study. Plasma O-glucuronide metabolite was not assessed.

The chronic (52-week) oral (gavage) study in M and F Beagle dogs given tapentadol once daily (10-80 mg/kg/day) confirmed the target organs toxicity seen in the shorter term oral and injection (IV and SC) studies in dog, in the CNS and cardiovascular system. One HD F was euthanized *in extremis* on dosing Day 12 due to convulsions on several days observed within 30 minutes after dosing. There were no necroscopic abnormalities in this dog. Convulsions were also seen in another HD F on multiple days throughout the dosing period up to Day 358, starting at 20-30 minutes after dosing and lasting for up to 5 hours. The convulsions were associated with paddling movements, muscle twitching, recumbency, tremor, labored breathing, and decreased activity, and were reversed with naloxone. No convulsions were observed during the recovery period. There were also treatment-related clinical signs consistent with tapentadol mu-opioid receptor agonist effects in the dog studies, including salivation, decreased activity, recumbency, vomiting, tremor, and occasional whimpering, and fearfulness, beginning at 15-30 minutes after dosing, and lasting for up to 5 hours. Reductions in food consumption (F at ≥30 mg/kg/day) and body weights (HD) were observed during the first several weeks of dosing.

ECG assessments in the chronic dog study revealed slight but statistically significant prolongation of the QT and corrected QT (Van de Water's and Fridericia's corrections) intervals in the 1 hour post-dose recordings in most of the HD dogs compared to baseline and control values throughout the treatment period. There were no other treatment-related ECG effects during the dosing period, and no ECG findings during the recovery period. Slight, minimal, treatment-related decreased partial thromboplastin time (PTT) values were found in the HD dogs, which were not reversible during the 4-week recovery period. The necropsy results were negative in the standard evaluations. However, special examination of brain showed minimal to slight focal gliosis with perivascular mononuclear cell infiltration in the medulla oblongata and/or pons in 2 M and F at 30 mg/kg/day, and in 1 HD F, with no correlation to seizure incidence, and are considered to be spontaneous, in agreement with the Sponsor. In the liver enzyme activity analysis, no tapentadol effects on cytochrome P450 content were found, but there were dose-related increases in O-deethylase activity in the F, and dose-related increases in N-demethylase

activity in the M and F. Also, 2-aminophenol glucuronyltransferase activity was decreased in the M and F dogs. The NOAEL in the 52-week toxicity study in dogs (10 mg/kg/day) represented systemic exposure to the parent drug that of approximately 0.05 times the exposure at the clinical maximum recommended human dose (MRHD) of 600 mg/day in a 70 kg patient, on an AUC basis, and 0.06 times on a Cmax basis, relevant to CNS and CV observations. The systemic exposure to the O-glucuronide metabolite at the NOAEL (10 mg/kg/day) in this study represented approximately 1.7X the clinical exposure at the MRHD. The exposure to the parent drug and metabolite at the NOEL for convulsions in this study represented approximately 0.4 and 5.2 times the clinical exposures to the parent drug and metabolite, respectively, at the MRHD on an AUC basis.

In summary, the main target organs of tapentadol toxicity in the repeated dose studies in dogs, most of which were commonly observed using several routes and durations of treatment, were the central nervous system (CNS), cardiovascular system (CV), gastrointestinal system (GI) and local toxicity in the intravenous and subcutaneous toxicity studies. The CNS clinical signs were similar in all of the studies across dose ranges given, and included salivation, restlessness, recumbency, decreased activity, rhinorrhea, panting, labored breathing, and tachypnea. In the b.i.d. study in the dogs given twice daily subcutaneous (SC) tapentadol injections for 3 months, the signs were more severe after the first than after the second daily dose, suggesting development of short term tolerance, a known phenomena with mu-opioid receptor agonist treatment. Also, the severity of the clinical signs decreased with increasing duration of treatment within several of the studies, further suggesting tolerance to opioid-induced behavioral effects. Most notable of the clinical signs were convulsions, observed in M and/or F dogs treated by SC injection for 3 months at ≥40 mg/kg/day (NOEL = 20 mg/kg/day SC), and by oral gavage at ≥50 mg/kg/day (NOEL = not determined) and ≥200 mg/kg/day (NOEL = 160 mg/kg) for 2 weeks, at 120 mg/kg/day for 13 weeks (NOEL = 80 mg/kg/day), and at 80 mg/kg/day for 52 weeks (NOEL = 30 mg/kg/day). No convulsions were observed in IV treated dogs at up to 7.5 mg/kg/day for up to 4 weeks duration. The convulsions were accompanied by paddling movements, tremors, and twitching. A possible relationship of the tremors observed in several studies in dogs to seizure activity was not investigated. There was no tolerance development to the treatment-related convulsant effect in the dogs. Although most of the dogs that convulsed either were sacrificed *in extremis* or received dose reductions following the seizures, a F given 80 mg/kg/day by oral gavage for 52 weeks showed convulsions on multiple days up to day 358 of dosing.

Tapentadol-related cardiovascular effects in the Beagle dog were indicated by QT prolongation in the ECG measurements across studies, at ≥8 mg/kg/day SC for 3 months (NOEL 4 mg/kg/day) particularly during the first week of treatment, at ≥35 mg/kg/day (Week 13) and 120 mg/kg/day (Week 1) in the 13-week gavage study (NOEL 10 mg/kg/day) and at 80 mg/kg/day in the 52-week oral gavage study (NOEL 30 mg/kg/day). No other ECG effects were found in the studies in dog. QT prolongation is probably associated with norepinephrine reuptake inhibition by tapentadol.

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