

## APPENDIX 2:

### Tabular Overview – Abuse Liability of Tramadol in Human Clinical Studies

Abuse Liability Clinical Studies								
(Country)	No. Subjects (tram/ref. drug/placebo)	Study Design	Study Duration	Tramadol Dose (mg)	Route of Admin.	Reference Drug and Dose	Variable Evaluated	Results
<b>Subjective, Behavioral and Psychophysiologic Variable Studies</b>								
<u>Healthy Volunteers</u>								
(Germany)	33 (22/--/11)	DB, PL, //, SD, MD	SD phase 36 hours  MD phase 4 days	SD phase 50, 100 mg;  MD phase 200, 400 mg	p.o.		Euphoria	No significant difference suggestive of euphoria between tramadol and placebo.
(Germany)	12 (12/12/12)	DB, PL, 3-period XO, SD	7 hours	100 mg	p.o.	Tilidine 100 mg/naloxone 8 mg	Euphoria	No significant difference between tramadol and placebo in subscales indicative of a euphoric effect. Scores indicate tramadol and tilidine/naloxone produced a depressant effect.
(Germany)	30 (15/--/15)	DB, PL	1 week	100 mg	i.m.		Euphoria, Drug-seeking behavior	No significant difference between tramadol and placebo for any euphoric subscale. Tramadol did not produce drug-seeking effects in normal subjects.
<u>Opiate Addicts</u>								
(U.S.)	6 (6/--/--)	Open-label, ascending-dose	12 hours	10-300 mg/kg	p.o., s.c.		Physical and subjective variables	Produced some morphine like subjective and behavioral effects. Was identified as an opioid-like drug. No reference drug makes results difficult to assess.
(Europe)	32 (16/16/--)	SB, //	5 days	400 mg Day 1, reduced by 100 mg Day 2-4	i.v.	Clonidine 0.15 mg/day i.v. plus 0.15 mg 3 times/day p.o.	Mitigating effects on withdrawal	Tramadol is able to ameliorate symptoms of opiate withdrawal. Superior to Clonidine. Subjects reported an initial unpleasant feeling following tramadol administration.
Protocol AA (U.S.)	12 (12/12/12)	DB, PL Latin square XO, SD	24 hours/dose	75, 150, 300 mg	i.m.	Morphine 15,30 mg	Subjective, behavioral, and psychophysiological response	Tramadol was not differentiated from placebo at 75 and 150 mg. Tramadol was identified as an opiate at 300 mg, but no other opioid effects were observed.

XO = Crossover; DB = Double-blind; MC = Multi-center; MD = Multiple-dose; NA = not applicable; NS = not specified; // = Parallel; PL = Placebo-controlled; SB = Single-blind; SD = Single-dose

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<b>Subjective, Behavioral and Psychophysiologic Variable Studies (continued)</b>								
<b>Opiate Addicts (continued)</b>								
Protocol TAA (U.S.)	12 (12/12/12)	DB, PL Latin square XO, SD	24 hours/dose	175, 350, 700 mg	p.o.	Oxycodone 20, 40 mg	Subjective, behavioral, and psychophysiological response	Tramadol and oxycodone produce a similar profile of effects which were opioid-like. Tramadol had slower onset and longer duration of effects. Lesser abuse potential for tramadol compared to other orally active opioids analgesics. Addicts gain no benefit in dissolving tablets for i.v. delivery.
Protocol TAB (U.S.)	6 (5/--/1)	DB, XO, ascending SD	24 hours/dose	300, 450, 600, 750 mg	p.o.		NA	Insufficient enrollment.
<b>Dependence Studies, Subjects with Chronic Pain</b>								
(Europe)	213 (213/--/--)	MC, Open-label, MD	3 weeks	100 mg	i.m.		Tolerance and withdrawal after naloxone i.v. 0.8 mg or 1.6 mg after 3 weeks of tramadol	No subject had scores indicative of moderate or severe dependence.
(Europe)	153 (153/--/--)	MC, Open-label, MD	3 weeks	up to 450 mg/day	p.o.		Tolerance and withdrawal after naloxone i.v. 1.6 mg or saline after 3 weeks of tramadol	Tolerance to tramadol does not develop.
(Europe)	200 (200/--/--)	MC, Open-label, MD	up to 6 months	NS	p.o.		Withdrawal after saline followed by 1.6 mg naloxone prior to study and naloxone i.v. 1.6 mg every 2 months	No development of dependence even after 6 months of treatment.
(Europe)	125 (125/--/--)	MC, Open-label, MD	up to 6 months	up to 400 mg	p.o.		Withdrawal after naloxone i.v. 1.6 mg prior to study and every 2 months	Dependence did not develop.

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<b>Dependence Studies, Subjects with Chronic Pain (continued)</b>								
24 month phase	16 (subgroup of 125 above)	Open-label, MD	up to 24 months	up to 400 mg	p.o.		Tolerance and withdrawal after naloxone 1.6 mg every 2 months	All not dependent.
Protocol TKB (U.S.) 3-day withdrawal phase	52 (36/16/--)	DB, //, MD	3 days	up to 400 mg	p.o.	APAP up to 400 mg ASA/Codeine up to 2.6 g ASA/240 mg Codeine	Withdrawal	During the 3-day withdrawal phase, comparison of WOW scores failed to reveal any significant differences.
<b>Psychomotor Performance</b>								
(Wales)	9 (9/9/--)	DB, 3-period XO, SD	3 hours	50, 100 mg	p.o.	Codeine 50 mg	Psychometric tests	No signif. difference for Digit Symbol Substitution Test or Paired Associate Test. At 100 mg dose, subjects took longer to complete Stroop Test.
(Germany)	17 (17/--/--)	Open-label, SD	4 hours	75 mg	p.o.		Eye hand coordination; bicycle ergometer	Physical work capacity and psychomotor performance were unaffected by tramadol in this study.

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