

U.S. Comments to the Tramadol Critical Review Document

Comments:

Page 1 3. *General pharmacology*

Replace the second and third italicized sentences with the following:

Tramadol is a synthetic, centrally acting opioid analgesic with a potent active opioid metabolite. Although its mode of action is not completely understood, from animal tests, at least two complementary mechanisms appear applicable: weak binding of parent and higher binding of M1 metabolite to μ -opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin.

Add: *Tramadol is a prodrug for the M1 metabolite which elicits strong μ -opioid effects.*

Delete the following both of which are in conflict with the product label and current information: *"It produces less respiratory depression than other opioids ..."* And *"It also reduces seizure... thresholds."*

The following warnings are in the product label and conflict with the above information:

1. Respiratory Depression: Tramadol should be administered cautiously in patients at risk for respiratory depression. In these patients, alternative non-opioid analgesics should be considered. When large doses of tramadol are administered with anesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose.

2. Seizures: Seizures have been reported in patients receiving tramadol within the recommended dosage range. Spontaneous post-marketing reports indicate that seizure risk is increased with doses of tramadol above the recommended range. Concomitant use of tramadol increases the seizure risk in patients taking:

- Selective serotonin reuptake inhibitors (SSRI antidepressants or anorectics),
- Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.), or
- Other opioids.
Administration of tramadol may enhance the seizure risk in patients taking:
 - MAO inhibitors,
 - Neuroleptics, or
 - Other drugs that reduce the seizure threshold.

Risk of convulsions may also increase in patients with epilepsy, those with a history of seizures, or in patients with a recognized risk for seizure (such as head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections). In tramadol overdose, naloxone administration may increase the risk of seizure.

Page 3 *Neuropharmacology*:

Add the following: Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to μ -opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ -opioid binding. Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound.

The affinity of the M1 metabolite to the μ -opioid receptor is 20 to 40 times greater than that of codeine and 160 to 300 times greater than tramadol, while the affinity of morphine is 7 to 12 times greater. (Frink, M.Ch., H.H. Hennies, W. Englberger, M. Haurand, and B. Wilffert, 1996, "Influence of Tramadol on Neurotransmitter Systems of the Rat Brain," *Arzneim. Forsch.*,46: 1029-36.)

The recent Grunenthal study (Grunenthal Department of Biochemical Pharmacology, Germany, Gillen et al 2000) was conducted to characterize tramadol and its metabolites M1, M2, M3 M4 and M5 at the cloned human μ -opioid receptor and concluded that the metabolite (+)-M1 is responsible for the μ -opioid-derived analgesic effect. The metabolite (+)-M1 showed the highest affinity ($K_i=3.4$ nM) to the human μ -opioid receptor, followed by (\pm)-M5 ($K_i=100$ nM), (-)-M1 ($K_i=240$ nM) and (\pm)-tramadol ($K_i=2.4$:M). Agonistic activity followed the following rank order of intrinsic efficacy: (+)-M1 > (\pm)-M5 > (-)-M1. The metabolites (\pm)-M2, (\pm)-M3 and (\pm)-M4 displayed weak affinity ($K_i>10$:M). (Gillen, C., M. Haurand, D. J. Kobelt, and S. Wnendt, 2000, "Affinity, potency and efficacy of tramadol and its metabolites at the cloned human μ -opioid receptor," *Naunyn-Schmiedeberg's Arch Pharmacol.* 362: 116-121.)

Page 3-4 *Respiratory effects*

Add the following: Study results (measurements of decreased tidal volumes and respiratory rates) vary with the dose of drugs administered. In addition, tramadol's peak effect is dependent upon formation of the M1 metabolite and is likely to occur at a later time than that of morphine, the active comparator.

Page 11 **6. Dependence and abuse potential B. Human Studies**

Preston et al study is not fully described. From the publication, the following is noted: Morphine 30 mg significantly increased scores on the Feel the Drug, High, and Like the Drug scales of the Subjects Drug Rating Questionnaire compared to placebo. Tramadol 300 mg produced statistically significant increases in ratings on Feel the Drug VAS; also, increases occurred on the High or Like the Drug scales, although not statistically significant. Neither drug produced significant scores on the Dislike the Effect scale. Morphine 30 mg and tramadol 300 mg produced significant increases in ratings of similarity to opiates.

The paragraph that describes the study by Zacny is a controlled human abuse laboratory study that belongs in the same section as the Preston et al. study. It should not be listed with reports describing the use and abuse of the drug. The conclusion in the Critical Review Document that tramadol did not impair psychomotor performance should include the sentence that morphine (mu-opioid, 1st active positive control) also did not impair psychomotor performance, but lorazepam (the CNS depressant benzodiazepine, 2nd active positive control) did impair psychomotor performance. Zacny concluded that when the placebo, tramadol, and lorazepam data from all subjects were analyzed, 100 mg tramadol induced miosis, and several subjective effects were increased significantly, including ratings of drug liking and "want to take again."