

### Column E Explanation

1. Registration Number: 48-R-0111
2. Number 1 of animals used in this study.
3. Species (common name) Dog of animals used in the study.
4. Explain the procedure producing pain and/or distress.

Animal was given a daily dose via oral gavage for 10 days prior to being found dead during post dose observations on study day 10. This animal had a seizure that was treatment on Day 1. In addition, at various times between study Days 1 and 10, body tremors, decreased activity, emesis, increased salivation and squinting eyes were recorded.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see Item 6 below)

No evidence of seizure was found after Day 1. None of the other observations were considered to require treatment or euthanasia.

6. What, if any; federal regulations require this procedure? Cite the agency, the code of Federal Regulations (CFR) title number and the specific section number (e.g. APHIS, 9 CFR 113.102):

The goal of this nonclinical toxicology evaluation was to characterize any toxic effects in regards to target organs, behavior, dose dependence, and exposure as required by 21 CFR 312.23 and ICH M3 (R2).

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4. Explain the procedure producing pain and/or distress.

Animal was given a daily test article dose via subcutaneous injection and an oral dose of and secondary formulation via oral gavage for 6 days prior to being found dead on study day 7. Animal had been observed to have body tremors, decreased activity, emesis, dehydration, squinting eyes and occasionally cold to touch at various times on study days 1-6.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see Item 6 below)

This animal was showing declining activity and food consumption over several days and was treated with food supplementation. Behavioral decline occurred rapidly on Day 6. This animal was treated aggressively on Day 6 with fluids and warming and was responsive and standing but was found dead early on Day 7. Had this animal not shown response to the fluids and warming, it would have been euthanized on that day.

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