

LOMUSTINE (CCNU) FDA-APPROVED HUMAN DRUG PRODUCT HAS BEEN REPORTED USEFUL FOR THE MANAGEMENT OF MALIGNANT TUMORS IN CATS

KEY POINTS:

- Lomustine (Gleostine™) has been reported to be an effective first- and second-line chemotherapy treatment for tumor-bearing cats.^{1,2}
- The optimal reported dosing schedule is 50–60 mg/m² PO every six weeks.^{3,4}
- Lomustine-induced hepatotoxicity in cats is minimal compared to that observed in dogs.
- Compounded lomustine capsules should not be used because recent findings indicate that many sources' capsules frequently contain less than 90% of the Active Pharmaceutical Ingredient (API) content and the API content often varies between capsules.⁵

BACKGROUND:

Lomustine (CCNU) is a nitrosourea chemotherapy agent that has been reported to be useful in the management of cats and dogs having malignant tumors, including mast cell tumors (MCT) and drug-resistant lymphomas. Lomustine has been shown to be useful as a single agent or in combination with other chemotherapy agents. In dogs, lomustine treatment may result in delayed but reversible hepatopathy; however, current data suggest that clinically-significant hepatopathy is uncommon in cats treated with lomustine. Lomustine is commercially available under the trade name Gleostine™ in 5 mg, 10 mg, 40 mg, and 100 mg capsules.⁶

Lomustine is frequently compounded. Recent findings have demonstrated that compounded capsules vary in API content, and the studies show that there is frequently a significant difference in API content in compounded capsules from source to source and capsule to capsule.



LOMUSTINE HAS BEEN REPORTED TO BE EFFECTIVE IN MANAGING CATS WITH MAST CELL TUMORS.¹

Study 1. In this retrospective study, 38 cats with MCT were treated with lomustine at a median administered dose of 56 mg/m² (range, 48 to 65 mg/m²).¹ Targeted doses were 50 mg/m² (22 cats) or 60 mg/m² (16 cats), and doses were rounded to the nearest available capsule size. Median number of doses was two (range, 1–12). Median interval between first and second lomustine treatments was six weeks (range, 3–12 weeks).

- Overall response rate (complete response + partial response [CR + PR]) was 50%.
 - 7 cats (18%) had complete response.
 - 12 cats (32%) had partial response.
- Median response duration was 168 days (range, 25–727 days).
- The most common toxicities were neutropenia and thrombocytopenia.
- Nadir in neutrophil count occurred at a median of 21 days (range, 7–28).
 - Median neutrophil count at nadir was 2,600 cells/μL (range, 0–17,948).
 - 3 cats (15%) experienced grade 3 or 4 neutropenia.
 - No cats developed signs of infection.

LOMUSTINE HEPATOXICITY HAS BEEN MINIMAL COMPARED TO THAT OBSERVED IN DOGS.²

Study 2. In this retrospective study, 29 tumor-bearing cats were treated with lomustine at an initial median dose of 44 mg/m² (range, 31–60 mg/m²) every 4–8 weeks.² Median cumulative dose was 204.7 mg/m² (range, 37–656 mg/m²).

- Observed clinical toxicities included decreased appetite, mild anorexia, occasional vomiting, and diarrhea.
- No cats experienced concurrent hematological toxicity, and no grade 3 gastrointestinal toxicity occurred.
 - All toxicities were resolved with conservative management.
- Increases in serum alanine transaminase (ALT) were observed in six cats (20.6%).
 - 4 cats (13.7%) had ALT increases prior to treatment with lomustine, and their ALT levels decreased with continued administration of lomustine.
 - 2 cats (6.8%) had increases in ALT after treatment.
- Data suggests lomustine-induced, clinically significant hepatopathy is uncommon in cats treated with lomustine even after high cumulative doses.

THE OPTIMAL REPORTED DOSING SCHEDULE IS 50–60 mg/m² PO EVERY SIX WEEKS.³

Study 3. In this prospective study to evaluate the tolerance of lomustine in cats, 25 tumor-bearing cats were treated at an orally-administered dosage of 50–60 mg/m² body surface area (BSA) every six weeks.³

- Neutropenia was the acute dose-limiting toxicity.
- Neutrophil nadir occurred 7–28 days after treatment (median, 14 days).
 - Median neutrophil counts at nadir were 1,000 cells/μL (range, 0–9,694).
- Neutropenia lasted up to 14 days (median, 7 days).
- 6 of the 20 cats (30%) that could be evaluated had partial response.
 - Stable disease was observed in 8 cats.
- No gastrointestinal, renal, or hepatic toxicities were noted during the observation period following lomustine treatment.

USING A “10-MG CAPSULE PER CAT” DOSING SCHEDULE FOR LOMUSTINE WAS NOT REPORTED AS AN OPTIMAL APPROACH FOR EFFECTIVE CANCER MANAGEMENT.⁴

Study 4. In this retrospective study, 20 cats with various malignant tumors were treated with lomustine (as a first-line agent or a salvage chemotherapeutic agent) every 21 days.⁴ All cats were dosed with 10-mg capsules regardless of body weight, resulting in a median dose of 42 mg/m² (range, 32–59 mg/m²) BSA. Median number of treatment cycles was three (range, 1–12).

- Cats receiving higher cumulative doses of lomustine had a greater likelihood of progressive neutropenia.
- Severe hematological toxicity was infrequent.
 - Out of the 97 administered doses of lomustine, there were three episodes of grade 4 neutropenia (3.1%), one episode of grade 3 neutropenia (1.0%), and one episode of grade 3 thrombocytopenia (1.0%).
- Overall response rate (CR + PR) was 25% (5 of 20 cats).
 - Cats treated in the upper 50% of the dose intensity range (45–59 mg/m²) had a statistically significant higher response rates than those treated in the lower 50% (32–45 mg/m²).
 - Authors discontinued the 10-mg per cat dosing as a standard in their clinic following this study.



COMPOUNDED LOMUSTINE VARIES AND MAY NOT REFLECT THE PRESCRIBED AMOUNT.⁵

Study 5. In this laboratory analysis, the lomustine drug content of five low-dose (10 mg) and five high-dose (40 mg) lomustine capsules from three compounders and one FDA-approved manufacturer was assessed by validated high-pressure liquid chromatography with ultraviolet detection method.⁵

- Gleostine™ capsules were all within the *a priori* acceptable limit of 90%–110% of the stated content (range, 104%–110%). [Figure 1]
- Compounded capsules were often outside the *a priori* acceptable limit of 90%–110% of the stated content (range, 78%–95%).
 - Compounded capsules had a failure rate of 40%–100%.
- Coefficients of variation for the compounded capsules were frequently high, while the variability for Gleostine™ capsules was relatively low. [Figure 2]
 - Coefficients of variation for the compounded capsules were 4.1%–16.7% for low-dose formulas and 1.1%–10.8% for high-dose formulas.
 - Coefficients of variation for Gleostine™ capsules were 0.5% for the low-dose and 2.3% for the high-dose formula.

Figure 1. Percentage of Capsules Within 90%–110% of Stated Content

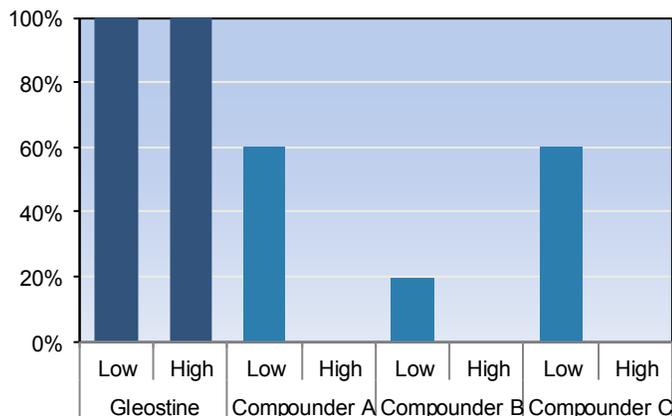
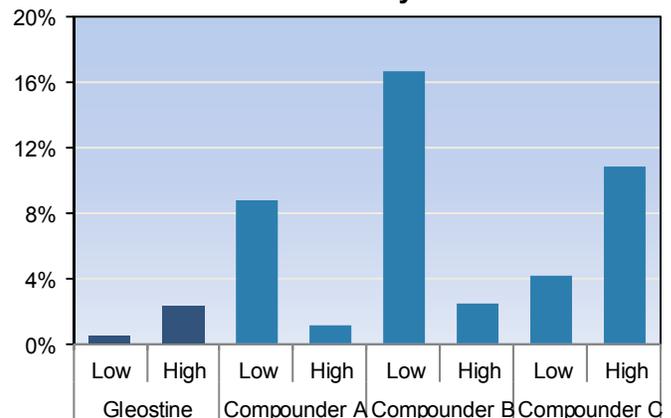


Figure 2. Coefficients of Content Variability



CONCLUSIONS

The high response rate and low occurrence of clinically-significant toxicity reported in these studies support lomustine as a treatment option for tumor-bearing cats. However, findings from the laboratory analysis indicate that compounded lomustine capsules have wide variability of API, and a majority of the tested compounded capsules were reported to contain less than 90% of the stated active drug content. Laboratory analysis further indicates that Gleostine™ capsules contain relatively uniform amounts of lomustine.

SUGGESTED DOSING REGIMENS FOR GLEOSTINE USE IN CATS

The data from these studies illustrate the potential benefits of using Gleostine™ in the treatment of malignant tumors, including mast cell tumors (MCT), in cats. The studies report that the optimal dosing scheme is 50–60 mg/m² every six weeks.

Body weight (kg)	BSA (m ²)	Dose using 50 mg/m ² scheme	Dose using 60 mg/m ² scheme	Dose rounded to the nearest available capsule size
3	0.21	10.5	12.6	10
4	0.25	12.5	15.0	15
5	0.29	14.5	17.4	15
6	0.33	16.5	19.8	20
7	0.37	18.5	22.2	20

Figure 3. Optimal Reported Dosing Scheme

Compounding to obtain the prescribed dosage is not recommended. Compounded lomustine has been shown to carry risks of inaccurately dosing a patient due to potential content failure and variability. Incorrect dosages could result in treatment failure, unpredictable results, and potentially enhanced neoplasia chemotherapy resistance. Therefore, using 5 mg and 10 mg Gleostine™ capsules to obtain the administered dosage is optimal. The above chart **[Figure 3]** provides examples of the appropriate dosing scheme for cats based on body weight and rounded to the nearest available capsule size.

¹ Rassnick, K. M., et al. (2008). Lomustine for treatment of mast cell tumors in cats: 38 cats (1999–2005). *JAVMA*, 232(8), 1200–1205.

² Musser, L. M., H. T. Quinn, & J. D. Chretien. (2012). Low apparent risk of CCNU (lomustine)-associated clinical hepatotoxicity in cats. *Journal of Feline Medicine and Surgery*, 14(12), 871–875.

³ Rassnick, K. M., et al. (2001). Phase I evaluation of CCNU (lomustine) in tumor-bearing cats. *J Vet Intern Med.*, 15, 196–199.

⁴ Fan, T. M., et al. (2002). Hematological toxicity and therapeutic efficacy of lomustine in 20 tumor-bearing cats: Critical assessment of a practical dosing regimen. *Journal of the American Animal Hospital Association*, 38, 357–363.

⁵ KuKanich, B., M. Warner, & K. Hahn. Analysis of lomustine drug content in FDA-approved drug product and compounded lomustine capsules. Publication pending.

⁶ NextSource Biotechnology. (2013). Lomustine (CCNU) [package insert]. Retrieved from <http://www.nextsourcebiotechnology.com/docs/pi/LomustineCCNU-PI.pdf>.