November 20, 2023

Zoetis Inc.
Attention: Dawn Cleaver, DVM
Associate Director, Regulatory Affairs
333 Portage St.
Kalamazoo, Michigan 49007

Re: **NADA 141-562**
Librela (bedinvetmab injection)

CMS # 665089

Dear Dr. Cleaver:

The Center of Veterinary Medicine (CVM) of the U.S. Food and Drug Administration (FDA) has reviewed the promotional communications on the Librela Professional Website[1] (LIB-00011R2), submitted by Zoetis under cover of Form FDA 2301. The website makes false or misleading claims and representations about the efficacy of Librela. Thus, the website misbrands Librela within the meaning of the Federal Food, Drug and Cosmetic Act (FD&C Act), making its distribution violative. 21 U.S.C. 352(a); 321(n); 331(a). See 21 CFR 202.1(e)(5). These violations are especially concerning from a public health perspective because the promotional communications create a misleading impression regarding the effectiveness of Librela, which is a veterinary drug in a novel therapeutic class.

Background

Below are the indication and summary of the most common risks associated with the use of Librela. According to the INDICATIONS section of the FDA-approved package insert (PI):

> LIBRELA is indicated for the control of pain associated with osteoarthritis in dogs.

The Adverse Reactions section of the PI for Librela contains the most common adverse reactions seen in the effectiveness field studies conducted for approval (i.e., the US Field study and European Union (EU) field study). In the US field study, the most common adverse reactions in the Librela treated group are as follows: urinary tract infection, bacterial skin infection, dermatitis, dermal mass, erythema, dermal cysts, pain on injection, inappropriate urination, and histiocytoma. In the EU Field study, the most common adverse reactions are as follows: increased blood urea nitrogen (BUN), lethargy, emesis, anorexia, lameness, and cough.

False or Misleading Claims

Prescription drug advertisements and labeling (promotional communications) misbrand a drug if they are false or misleading in any particular (see 21 U.S.C 352(a)). The determination of

[1] Librela Professional Website found at https://www.librelavetteam.com (last accessed 11.17.2023).

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whether a promotional communication is misleading includes, among other things, not only representations made or suggested in the promotional communication, but also the extent to which the promotional communication fails to reveal facts material in the light of its representations or material with respect to consequences that may result from the use of the drug as recommended or suggested in the promotional communication (21 U.S.C 321(n) and 21 CFR 202.1(e)(5))**.**

Misleading Efficacy Claims

The Librela Professional Website, under the "Efficacy" section, includes graphs presenting the results of the US field study and the EU field study. Each graph presents the "% Success Rate Measured by CBPI"[2] for both the Librela-treated group and a placebo group at various timepoints (7, 14, 28, 42, 56, and 84 days post treatment). According to the graphs on the website, a p-value ≤ 0.05 was marked on Days 42, 56, and 84 in the US field study and on Days 7, 14, 28, 42, 56 and 84 in the EU field study. A p-value is generally understood in the scientific community to indicate statistical significance if it is less than 0.05.

These graphs are misleading regarding the efficacy of Librela. When multiple endpoints are tested statistically, the Type I error rate (the probability of erroneously concluding an effect when the truth is that there is no effect) may be inflated[3]. According to the Effectiveness section of the PI, the primary effectiveness endpoint for both the US and EU field studies was treatment success on Day 28, and treatment successes for the remaining time points were identified as secondary endpoints. Neither the US nor the EU study was designed to make statistical conclusions regarding effectiveness at study days other than the primary endpoint on Day 28. When more than one endpoint is analyzed in a single trial, if adjustments are not made to account for the potential inflation of Type I error rate, the likelihood of making false conclusions about a drug's effects with respect to one or more of those endpoints could increase. Therefore, the p-values associated with the analyses of the multiple secondary endpoints should not be interpreted as evidence of statistically significant differences. The inclusion of a p-value (i.e., p ≤ 0.05) in the graphs on the website for the secondary time points creates a misleading impression about the efficacy of Librela, undermining the ability of the reader to understand the study results presented.

We acknowledge that the third reference included in the footnotes of the Librela Professional Website is an article on the results from the EU study published in 2021[4]. Table 4 of the article summarizes the statistical comparison of proportions of success at each study day evaluated and includes the p-values at each timepoint. While the p-values noted in Table 4 are ≤ 0.05, this does not justify the inclusion of these values in the EU graph on the website because, as stated previously, adjustments were not made to the study protocol to account for the potential inflation of Type I error rate. Providing this article as an explanation for the p values on the EU graph does not mitigate the misleading impression created by the graphs on the website. Some veterinarians may not recognize that there was no discussion of adjusting for multiple endpoint

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[2] The CPBI is an owner-completed questionnaire designed to quantify the severity of chronic pain and its impact on routine activities in companion dogs.

[3] Guidance for Industry. "Multiple endpoints in clinical trials guidance for industry." Food and Drug Administration Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) (2022)

[4] Corral, Maria J., et al. "A prospective, randomized, blinded, placebo-controlled multisite clinical study of bedinvetmab, a canine monoclonal antibody targeting nerve growth factor, in dogs with osteoarthritis." Veterinary anaesthesia and analgesia 48.6 (2021): 943-955. doi:10.1016/j.vaa.2021.08.001

testing in the article and, therefore, the p-values from the other study days must be interpreted with the appropriate caution due to the potential for inflated Type I error. In addition, the website does not supply context to explain how to interpret the p values, specifically that Day 28 was pre-specified as the primary endpoint and that the p-values for the other days should not be interpreted in the same manner as the Day 28 result.

The Freedom of Information (FOI) summary acknowledges the numerical differences observed in the treatment success rates on non-primary timepoints. For the US field study, the FOI summary states, “Although this study did not demonstrate treatment success based on the established primary effectiveness outcome measure at Day 28, the treatment success rate and the **numerical difference** between the success rates of the two groups from Day 42 (14 days after the second treatment) onward demonstrate a **clinically relevant effect** in the Librela™ group compared to the control group” (emphasis added). The FOI summary also reports the results of hypothesis testing on Day 28 in the EU study: “The primary effectiveness variable was successful and met statistical significance at Day 28 (P = 0.0018).” The p-values from the secondary timepoints cannot be interpreted in the absence of pre-specified adjustments to the study protocol and were therefore not included in the FOI summary.

Conclusion and Requested Action

For the reasons discussed above, the website misbrands Librela within the meaning of the FD&C Act and make its distribution violative. 21 U.S.C. 352(a), 321(n), 331(a). See 21 CFR 202.1(e)(5).

This letter notifies you of our concerns and provides you with an opportunity to address them. CVM requests that Zoetis cease any violations of the FD&C Act. Please submit a written response to this letter within 15 working days from the date of receipt, addressing the concerns described in this letter, listing all promotional communications for Librela that contain representations like those described above, and explaining any plan for discontinuing use of such communications, or for ceasing distribution of Librela.

If you believe that your products are not in violation of the FD&C Act, please include in your submission to us your reasoning and any supporting information for our consideration within 15 working days from the date of receipt of this letter.

The concerns discussed in this letter do not necessarily constitute an exhaustive list of potential violations. It is your responsibility to ensure compliance with each applicable requirement of the FD&C Act and FDA implementing regulations.

Please direct your response to the undersigned at the Food and Drug Administration, Center for Veterinary Medicine, Division of Pharmacovigilance and Surveillance, HFV-240, 12225 Wilkins Ave, MPN II Room E474, Rockville, Maryland 20852. Please send a courtesy copy by email to CVMSurveillance@fda.hhs.gov. All correspondence should include a subject line that clearly identifies the submission as a Response to Untitled Letter # 665089.

If you have any questions, please contact Dr. Christopher Loss by email at christopher.loss@fda.hhs.gov.

Sincerely,

Linda A. Walter-grimm -S

Digitally signed by Linda A. Walter-grimm -S
Date: 2023.11.20 07:50:24 -05'00'

Linda Walter-Grimm, DVM
Director, Division of Pharmacovigilance and Surveillance
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