U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR VETERINARY MEDICINE

May 24, 2024

CVM File: G-150438

Elanco US, Inc.
PO Box 708, 2500 Innovation Way
Greenfield, IN, 46140
FEI: 3012761605

Attn: Dr. G. Allen Bridges
Director - Global Nutritional Health Regulatory
allen.bridges@elancoah.com

Dear Dr. Bridges,

On June 8, 2023, Elanco US, Inc. ("Elanco" or "you") submitted a request for consultation with CVM regarding 3-nitrooxypropanol (3-NOP), marketed as Bovaer® 10, a new substance for use in animal food. Based on your letter, Bovaer® 10 is the market formulation which contains the active substance, 3-NOP. You also state that 3-NOP is intended for the reduction of methane emissions per pound of dry matter (DM) intake when incorporated at 27.2-36.3 mg 3-NOP per pound (60-80 mg per kilogram) of DM in the total mixed ration of lactating dairy cows.

Based on the information provided in your letter, Bovaer® 10 is an article (other than food) intended to affect the structure or any function of the body of an animal, and therefore it is a drug.[1] However, the Center for Veterinary Medicine (CVM) has considered whether it intends to exercise enforcement discretion with regard to certain requirements applicable to animal drugs for Bovaer® 10 – including requirements regarding new animal drug approval, pharmaceutical current Good Manufacturing Practice, adverse event reporting, labeling[2], drug establishment registration and drug product listing. CVM has considered whether refraining from enforcement of these requirements at this time would be appropriate based on whether Bovaer® 10 poses a low risk to humans and animals and whether the data show that the product has the intended effect.

CVM reviewed the information you submitted on June 8, 2023, and subsequent correspondence on January 31, 2024, that addressed the safety, intended effect and the quantity of the article required to produce the intended effect, manufacturing, labeling for the article, and other relevant information. Based on a review of your data and the characteristics of your product, FDA has no questions at this time regarding whether Bovaer® 10 will achieve its intended effect and is expected to pose low risk to humans

[1] Section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) defines "drug," in relevant part, as articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and/or articles (other than food) intended to affect the structure or any function of the body of man or other animals.

[2] We note that drugs, including animal drugs, are subject to the prohibition on false or misleading labeling under section 502(a) of the FD&C Act and to the requirements for prescription-drug advertising set forth in section 502(n) of the FD&C Act. Although FDA intends to exercise enforcement discretion with respect to certain animal-drug requirements, as noted above, FDA expects compliance with these labeling and advertising requirements under the statute.

or animals under the conditions of its intended use. This product demonstrated a reduction of methane gas emissions per pound of dry matter intake when incorporated at 27.2-36.3 mg 3-NOP per pound (60-80 mg per kilogram) of DM in the total mixed ration of lactating dairy cows. Data were not evaluated for other gas emissions.

Although Bovaer® 10 is an unapproved drug, at this time we do not intend to initiate enforcement action with respect to the drug requirements listed above for Elanco's marketing Bovaer® 10 or use provided FDA continues to have no questions or public health concerns about Bovaer® 10. Based on our prior discussions, we understand that you intend to take the following steps:

Standards

- Manufacture, process, pack, and/or hold Bovaer® 10 under conditions comparable to the standards of Title 21, Code of Federal Regulations, part 507, "Current Good Manufacturing Practice, Hazard Analysis, and Risk-Based Preventive Controls for Food for Animals."

Reporting

- Obtain an FDA Establishment Identifier (FEI) for Bovaer® 10 manufacturing facility and provide that information to animalfood-premarket@fda.hhs.gov.[3]
- Report any substantive changes to your manufacturing procedures or methods, or the information in your letter, that could impact product characterization, safety, or effectiveness to CVM at animalfood-premarket@fda.hhs.gov prior to implementing them.

Adverse Event and Product Problem Reporting

- Report electronically through the Safety Reporting Portal[4] within 24 hours after you determine that, due to an issue or problem with Bovaer® 10, there is a reasonable probability that the use of, or exposure to, Bovaer® 10 or product containing Bovaer® 10 will cause serious adverse health consequences or death to humans or animals.
    - Please include a reference to "CVM Letter G-150438" in the "Enter a title to help you identify your report" field of the report questionnaire.
- Electronically submit any adverse events reports, product defects, or consumer complaints received or otherwise obtained for Bovaer® 10 through the Safety Reporting Portal within 30 days of receipt.[5]
    - The adverse event and/or product defect information in the portal will use the appropriate voluntary reporting path depending upon the relevant category of animal.
    - When reporting, please include a reference to "CVM Letter G-150438" in the "Enter a title to help you identify your report" field of the report questionnaire.
- Maintain a log of all complaints (including all adverse event reports and product defect reports, and consumer complaints) received, and make the log and related documents available to FDA when requested.

Labeling

You have shared a representative label with CVM (see attached).

You may be responsible for other federal, state, or local requirements that are not addressed by this correspondence. Our intent not to enforce certain animal drug requirements is based on our current understanding of the product from the information you provided. This letter does not alter the status of Bovaer® 10 as an animal drug and you should consider this fact when making decisions regarding

[3] The FEI is an FDA system-generated number used to identify a firm. To look up an existing FEI or access the FEI Portal FAQ page (including how to use the portal and how to request an FEI), refer to https://www.accessdata.fda.gov/scripts/feiportal/.
[4] Electronic reporting should be through the Safety Reporting Portal's Livestock "Product Problem" path found at https://www.safetyreporting.hhs.gov/SRP2/en/Home.aspx?sid=9da0e4e2-3977-4f19-bbfb-363225f26a70; please contact CVM for specific details on how to report.
[5] For more information about reporting related events to FDA CVM, see https://www.fda.gov/animal-veterinary/safety-health/report-problem.

distributing Bovaer® 10. FDA has the right to take action under its authorities, and we may reevaluate our intent to refrain from enforcement if we become aware of information that raises a concern about the safety or effectiveness of Bovaer® 10 or under any other circumstance covered by our authorities. In such a case, the product would be treated as an unapproved new animal drug.[6]

If you submit correspondence relating to this letter, you should reference the date and the CVM File G-150438 identifier found at the top of this letter. If you have any questions, please contact Dr. David Edwards by email at: David.Edwards@fda.hhs.gov.

Sincerely,

/s/
Neal Bataller, ME, DVM
Director, Division of Drug Compliance
Office of Surveillance and Compliance

Attachment – Bovaer® 10 Label

[6] The article may be considered an unsafe new animal drug under section 512(a) of the FD&C Act and, therefore, an adulterated drug under section 501(a)(5) of the FD&C Act. Further, any food that bears or contains the article may be considered adulterated under section 402(a)(2)(C)(ii) of the FD&C Act.

Attachment

Bovaer® 10

(3-Nitrooxypropanol)
For further manufacture of feed for reduction of methane gas emissions per pound of dry matter intake in lactating dairy cows.

GUARANTEED ANALYSIS:
3-nitrooxypropanol, minimum……10% (w/w)
Silicon dioxide, maximum……60% (w/w)

Ingredients: Silicon dioxide, propylene glycol, 3-nitrooxypropanol

Directions for Use:
Thoroughly mix Bovaer 10 into a total mixed ration at 540-720 g/ton of complete feed (100% dry matter basis) to provide 27.2-36.3 mg 3-nitrooxypropanol per pound (60-80 mg per kilogram) of dry matter intake. Bovaer 10 can be incorporated into a premix then included in the total mixed ration to ensure adequate uniformity.

Feed continuously to lactating dairy cows. Effectiveness was demonstrated in a total mixed ration containing 27.3-31.8% neutral detergent fiber and 5.2-5.8% crude fat. Dietary factors influence effectiveness, and feeding diets outside of these ranges may result in reduced effectiveness.

Data supporting effectiveness has been evaluated when fed for no more than 105 days. Methane gas emissions were measured for individual animals. Data were not evaluated at the herd, farm, or larger scale. Data were not evaluated for other gas emissions. Milk production, feed efficiency, and milk solids have not been evaluated.

Caution:
Do not feed undiluted. For use in feed for lactating dairy cows only. Not for use in dry dairy cows, bulls, replacement heifers or bulls, growing cattle, or other ruminant species because safety and effectiveness have not been evaluated in these animals. Silicon dioxide from all sources cannot exceed 2 percent by weight of the complete feed.

A decrease in dry matter intake may be observed in some animals.

Warning:
Not for human use. Caution should be exercised when handling this product. 3-nitrooxypropanol may damage male fertility and reproductive organs, is potentially harmful when inhaled, and is a skin and eye irritant. Personal protective gear, including eye wear, a dust mask, and impervious gloves, should be worn when handling this product. Operators should wash hands after handling. If accidental eye exposure occurs, rinse eyes thoroughly with water. The safety data sheet contains more detailed occupational safety information.

To report suspected adverse reactions, contact Elanco US Inc. at 1-800-428-4441 or FDA at https://www.safetyreporting.hhs.gov/.

Best Used By: 36 months after the date of manufacture
Storage Information: Store in a dry location at temperatures below 25°C (77°F). Keep package closed.

Net Weight 20 kg (44 lb)

Manufactured for
Elanco US Inc.
2500 Innovation way
Greenfield, IN 46410
1-800-428-4441

LIMITED WARRANTY STATEMENT. The Company's sole and exclusive warranty is that the product is free from defects in materials and workmanship at the time of sale. THE COMPANY MAKES NO OTHER WARRANTY, EXPRESSED OR IMPLIED. TO THE EXTENT CONSISTENT WITH APPLICABLE LAW, THE COMPANY DISCLAIMS ANY IMPLIED WARRANTIES, INCLUDING MERCHANTABILITY. The Company shall not be liable for any incidental or consequential damages. To the extent consistent with applicable law, the Company's maximum liability shall be limited to the purchase price of the product.

Country of Origin: Germany