February 5, 2025

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

Re: NADAs 141-562 Librela™ (bedinvetmab injection), 141-546 Solensia™ (frunevetmab injection), 141-502 Revolution® Plus (selamectin and sarolaner topical solution)

CMS#: 691206

Dear Dr. Cleaver:

The U.S. Food and Drug Administration (FDA) has reviewed your promotional communications found on the Zoetis Petcare YouTube Channel.[1] Several videos on the website make false or misleading claims and representations about the risks associated with several new animal drugs, including Librela, Solensia, and Revolution Plus. Thus, the website misbrands Librela, Solensia, and Revolution Plus within the meaning of the Federal Food, Drug, and Cosmetic Act (FD&C Act). FD&C Act section 502(a) [21 U.S.C. 352(a)]; section 502(n) [21 U.S.C. 352(n)]; section 201(n) [21 U.S.C. 321(n)]; and 21 CFR 202.1(e)(5). Introducing or delivering misbranded new animal drugs for introduction into interstate commerce violates section 301(a) of the FD&C Act [21 U.S.C. § 331(a)]. These violations are especially concerning from a public health perspective because the promotional communications create a misleading impression regarding the safety and effectiveness of Librela, Solensia, and Revolution Plus.

Product Information[2]

Librela

According to the Indication section of the FDA-approved package insert (PI):

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

The Contraindications section of the PI states, in part, “LIBRELA should not be used in breeding dogs or in pregnant or lactating dogs.” The User Safety Warnings subsection of the PI states, in part, “Hypersensitivity reactions, including anaphylaxis, could potentially occur in the case of accidental self-injection,” and “Pregnant women, women trying to conceive, and breastfeeding women should take extreme care to avoid accidental self-injection.” The Precautions section of the PI states, in part, “Administration of monoclonal antibodies may

[1] Zoetis Petcare YouTube Channel found at Zoetis Petcare - YouTube (last accessed 2.4.2025).
[2] This section does not include all the safety and risk information in the package insert for each product and does not necessarily represent the risk information that should be included in the promotional communication(s) cited in this letter.

U.S. Food and Drug Administration
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be associated with hypersensitivity reactions and delayed hypersensitivity reactions," and "Treatment with LIBRELA may result in the formation of anti-bedinvetmab antibodies and potentially loss of product effectiveness (see **IMMUNOGENICITY**)."

The Adverse Reactions section of the PI for Librela contains the most common adverse reactions seen in the effectiveness field studies conducted for approval in the United States and Europe. In the United States field study, the most common adverse reactions in the Librela treated group were: urinary tract infection, bacterial skin infection, dermatitis, dermal mass, erythema, dermal cyst(s), pain on injection, inappropriate urination, and histiocytoma. In the European field study, the most common adverse reactions were: increased blood urea nitrogen (BUN), lethargy, emesis, anorexia, lameness, and cough.

Solensia

According to the Indication section of the FDA-approved PI:

> SOLENSIA is indicated for the control of pain associated with osteoarthritis in cats.

The Contraindications section of the PI states, in part, "SOLENSIA should not be used in breeding cats or in pregnant or lactating queens because it may pass through the placental blood barrier and be excreted in milk." The User Safety Warnings subsection of the PI states, in part, "Hypersensitivity reactions, including anaphylaxis, could potentially occur in the case of accidental self-injection," and "Pregnant women, women trying to conceive, and breastfeeding women should take extreme care to avoid accidental self-injection." The Precautions section of the PI states, in part, "Administration of mAbs[3] may be associated with hypersensitivity reactions and delayed hypersensitivity reactions," and "Administration of SOLENSIA may be associated with scabbing on the head and neck, dermatitis, and pruritus; however, preapproval data suggest that these signs do not require cessation of SOLENSIA administration (see **ADVERSE REACTIONS** and **TARGET ANIMAL SAFETY**)." The Precautions section also states "Treatment with SOLENSIA may result in the formation of anti-frunevetmab antibodies and potentially the loss of product effectiveness (see **Immunogenicity**)."

The Adverse Reactions section of the PI for Solensia contains the most common adverse reactions seen in the effectiveness field study conducted for approval, which include vomiting, injection site pain, diarrhea, abnormal behavior and behavioral disorders, renal insufficiency, anorexia, lethargy, dermatitis, alopecia, dehydration, lameness, pruritus, weight loss, scabbing on head/neck, gingival disorder, bacterial skin infection, and otitis externa.

Revolution Plus

According to the Indications section of the FDA-approved PI:

> REVOLUTION PLUS is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis*. REVOLUTION PLUS kills adult fleas (*Ctenocephalides felis*) and is indicated for the treatment and prevention of flea infestations, the treatment and control of tick infestations with *Amblyomma americanum* (lone star tick), *Amblyomma maculatum* (Gulf Coast tick), *Dermacentor variabilis* (American dog tick), and *Ixodes scapularis* (black-legged tick), the treatment and control of ear mite (*Otodectes cynotis*) infestations, and the treatment and control of roundworm

[3] The abbreviation "mAbs" stands for "monoclonal antibodies."

(*Toxocara cati*) and intestinal hookworm (*Ancylostoma tubaeforme*) infections for one month in cats and kittens 8 weeks and older, and weighing 2.8 pounds or greater.

The Humans Warnings subsection of the PI states, in part, "**Do not come into contact with or allow children to contact the application site until 4 hours post application**" and **"In humans, REVOLUTION PLUS may be irritating to skin and eyes**." The PI contains additional adverse event, warning, precaution, and contraindication information unrelated to this letter.

False or Misleading Risk Presentation

Prescription drug advertisements and labeling (promotional communications) misbrand a drug if they are false or misleading in any particular. *See* FD&C Act section 502(a),(n) (21 U.S.C 352(a),(n)). The determination of 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. FD&C Act section 201(n) (21 U.S.C 321(n)) and 21 CFR 202.1(e)(5).

Librela

The Zoetis Petcare YouTube Channel contains multiple videos purporting to show footage before and after treatment with Librela[4] that contain no risk information, while the visual representations show benefits - such as improved gait or walking - that is clearly attributed to Librela. We acknowledge that there is Important Safety Information (ISI) in a text box below the videos. However, the ISI information is not visible unless the viewer clicks on the "more" button to expand the text box. These videos are misleading as they lack fair balance because they fail to present information relating to contraindications, warnings, precautions, and adverse reactions to the drugs with a prominence and accessibility reasonably comparable with the presentation of information relating to the benefits (*see* 21 CFR 202.1(e)(5)(ii)). Specifically, the benefits are presented in the video, but the risk information is not.

Librela and Solensia

A video for Librela[5] and two videos for Solensia[6] identified as "TV commercials" on the YouTube Channel contain voice-overs that discuss risk information related solely to the potential for self-injection by veterinary professionals who administer the drug. However, there is no information in the voice-overs that discusses the risk to the animal although these risks are identified in the PI. These videos are misleading because they are aimed at the pet owner, yet they omit important safety and risk information for the animal species the drug is approved to treat. While there is some animal-related risk information included in superimposed text at the bottom of the video screen for a portion of the video, 21 CFR

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[4] Librela videos before and after treatment: https://www.youtube.com/watch?v=5l3w3uD9mvs, https://www.youtube.com/watch?v=6tRqIorWYdg, https://www.youtube.com/watch?v=DG0TjQrghBM, https://www.youtube.com/watch?v=ZzHENCK1CNA, https://www.youtube.com/watch?v=611aEp2RsIc, https://www.youtube.com/watch?v=pUduWJ_Ooyg, https://www.youtube.com/watch?v=BYU0y8UNZ7c (last accessed 2.4.2025).
[5] Librela TV Commercial: https://www.youtube.com/watch?v=8MLTLRvzhKg (last accessed 2.4.2025).
[6] Solensia TV Commercials: https://www.youtube.com/watch?v=zHtGhKfhCGU, https://www.youtube.com/watch?v=TbFG8DAOxcQ (last accessed 2.4.2025).

202.1(e)(1) requires information relating to the major side effects and contraindications be present in the audio or audio and visual part of the advertisement broadcast through television.

Further, the text in the 60 second Solensia video (SLN-00009) related to safety is not presented with a prominence and readability reasonably comparable with the text in the video related to effectiveness (see 21 CFR 202.1(e)(7)(viii)). The safety text is small and difficult to read compared to the effectiveness claims (e.g., "77% of cat owners experienced improvement in their cat's pain"). We acknowledge that there is animal-related risk information included in the description panel below the video, but to see this information the viewer must click the "more" button. The presence of this risk information in this location is not apparent because the preview for the description panel only contains effectiveness information.

Revolution Plus

A video for Revolution Plus titled "How to Apply REVOLUTION PLUS to Your Cat"[7] includes the following language in the audio and visual portion of the video: "And unlike other products, you can keep close to your cat even after applying Revolution Plus. No separation needed." This language occurs concurrently with a visual of a child hugging the cat, with the child's arm near the area where the product should be applied. However, the Human Warnings section of the Revolution Plus PI states, "**Do not come into contact with or allow children to contact the application site until 4 hours post application.**" The language used in the video is therefore misleading because it implies that there are no safety concerns regarding humans interacting with any part of the cat after application of Revolution Plus, which is in direct conflict with the information in the Human Warnings section.

Conclusion and Requested Response

For the reasons discussed above, the YouTube Channel misbrands Librela, Solensia, and Revolution Plus within the meaning of the FD&C Act. FD&C Act section 502(a), (21 U.S.C. 352(a)); section 502(n) [21 U.S.C. 352(n)]; section 201(n) (21 U.S.C. 321(n)); and 21 CFR 202.1(e)(5). Introducing or delivering misbranded new animal drugs for introduction into interstate commerce violates section 301(a) of the FD&C Act [21 U.S.C. § 331(a)].

This letter notifies you of our concerns and provides you with an opportunity to address them. 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, Solensia, and Revolution Plus that contain representations like those described above, and explaining any plan for discontinuing use of such communications, or for ceasing distribution of Librela, Solensia, and Revolution Plus.

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.

This letter is not intended to be an all-inclusive statement of violations that may exist in connection with your products. You are responsible for investigating and determining the causes of any violations and for preventing their recurrence or the occurrence of other

[7] How to Apply Revolution Plus to Your Cat video: https://www.youtube.com/watch?v=HFEKYcXFWPM (last accessed 2.4.2025).

violations. It is your responsibility to ensure that your firm complies with all requirements of federal law, including FDA regulations.

Please direct your response to the undersigned at the Food and Drug Administration, Center for Veterinary Medicine, Division of Pharmacovigilance and Surveillance, 12225 Wilkins Ave, MPN II Room E436, 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 # 691206

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: 2025.02.05 10:10:24 -05'00'

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