Date of Approval: September 19, 2025

FREEDOM OF INFORMATION (FOI) SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION (NADA)

NADA 141-585

Zenrelia™

(ilunocitinib tablets)

Dogs

This supplement provides for revisions to the boxed warning and Animal Safety Warnings.

Sponsored by:

Elanco US Inc.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 141-585

B. Sponsor

Elanco US Inc.
450 Elanco Circle
Indianapolis, IN 46221

Drug Labeler Code: 058198

C. Proprietary Name

Zenrelia™

D. Drug Product Established Name

Ilunocitinib tablets

E. Pharmacological Category

Immunosuppressant

F. Dosage Form

Tablet

G. Amount of Active Ingredient

4.8, 6.4, 8.5, or 15 mg of ilunocitinib per tablet

H. How Supplied

Zenrelia™ (ilunocitinib tablets) is available in scored tablets in four strengths: 4.8 mg, 6.4 mg, 8.5 mg, and 15 mg. Each tablet strength is available in 10 and 30 count blister packages and 90 count bottles.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

The dose of Zenrelia™ (ilunocitinib tablets) is 0.27 to 0.36 mg ilunocitinib/lb (0.6 to 0.8 mg ilunocitinib/kg) body weight, administered orally, once daily, with or without food.

K. Route of Administration

Oral

L. Species

Dogs

M. Indication

Zenrelia™ is indicated for control of pruritus associated with allergic dermatitis and control of atopic dermatitis in dogs at least 12 months of age.

N. Effect of Supplement

This supplement provides for revisions to the boxed warning and Animal Safety Warnings.

II. EFFECTIVENESS

A. Dosage Characterization

This supplemental approval does not change the previously approved 0.6 to 0.8 mg/kg (0.27 to 0.36 mg/lb) dose, given orally once a day. The FOI Summary for the original approval of NADA 141-585 dated September 19, 2024, contains dosage characterization information for dogs.

B. Substantial Evidence

The Food and Drug Administration (FDA) did not require effectiveness studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-585 dated September 19, 2024, contains a summary of studies that demonstrate effectiveness of the drug for dogs.

III. TARGET ANIMAL SAFETY

The safety data to support the original approval of Zenrelia™ (NADA 141-585; refer to the FOI summary, dated September 19, 2024) included the study entitled "The Effect of Oral LY3411067 on the Response to Primary Vaccination in Dogs. (Study No. ELAVV200035)". In this study, one dog was euthanized due to lethargy, depression, poor body condition, and weakness. The histopathology evaluation in this dog revealed marked necrotizing hepatitis and pancreatitis and evidence of systemic endotoxemia. Prominent intranuclear inclusion bodies were found in the liver and pancreas, consistent with adenoviral infection. Based on the information available during the original approval, it was concluded that this dog acquired a vaccine-induced adenoviral hepatitis and pancreatitis secondary to Zenrelia™-induced immunosuppression, which resulted in a boxed warning on the labeling regarding the risk of vaccine-induced disease. Additionally, another dog was euthanized during the study that was found to have a colonic intussusception, potentially related to a clinical *Cystoisospora canis* infection.

To further elucidate the adenoviral etiology, a nested polymerase chain reaction (PCR) method[1] was developed and validated for conducting a one-time study to detect the presence of canine adenovirus type 1 (CAV-1) (the causative agent for infectious canine hepatitis [ICH]) and CAV-2 (the virus present in the administered vaccination) in canine liver tissue. The CAV-1 and CAV-2 primers were demonstrated to be specific for the respective canine adenovirus serotypes.

Using the PCR method, formalin-fixed paraffin embedded liver tissues were tested from the two dogs euthanized during the vaccine response study; none of the liver tissues from the other dogs were tested. The CAV-1 PCR results were confirmed by nucleic acid sequencing to align with the reference genome of CAV-1 (National Center for Biotechnology Information (NCBI) Reference Sequence: AC_000003.1) but not CAV-2 (NCBI Reference Sequence: AC_000020.1).

Because the nested PCR method is qualitative and does not quantify the amount of virus present nor confirm the presence of live virus, no conclusions could be made about the abundance or virulence of the viruses nor which viruses were causing clinical signs of infection. However, the presence of another adenovirus in the liver tissues suggests that the fatal adenoviral hepatitis and pancreatitis was not vaccine induced and may have been due to a natural adenoviral infection, such as infectious canine hepatitis. Given the presence of *Cystoisospora canis* infections in multiple dogs, a natural adenoviral infection, such as ICH, could have occurred. The totality of evidence supports removal of the risk of fatal vaccine-induced disease from modified live virus vaccines from the labeling.

IV. HUMAN FOOD SAFETY

This drug is intended for use in dogs. Because this new animal drug is not intended for use in food-producing animals, FDA did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Zenrelia™:

Not for use in humans. Keep this drug out of the reach of children. Wash hands immediately after handling tablets. In case of accidental ingestion, seek medical attention immediately.

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 514. The data demonstrate

[1] Modified from Walker, D., Fee, S. A., Hartley, G., Learmount, J., O'Hagan, M. J., Meredith, A. L., de C Bronsvoort, B. M., Porphyre, T., Sharp, C. P., & Philbey, A. W. (2016). Serological and molecular epidemiology of canine adenovirus type 1 in red foxes (*Vulpes vulpes*) in the United Kingdom. *Scientific reports*, *6*, 36051. https://doi.org/10.1038/srep36051.

that Zenrelia™, when used according to the label, is safe and effective for the effect of supplement in the General Information Section above.

A. Marketing Status

This product may be dispensed only by or on the order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to rule out other diseases in the diagnosis of allergic and atopic dermatitis, and to monitor and ensure the safe use of the product, including treatment of any adverse reactions and determining the appropriate time to administer vaccines.

B. Exclusivity

Any applicable exclusive marketing rights and exclusivity under the original approval for this drug continue.

C. Supplemental Applications

This supplement is a Category II supplement as defined in (21 CFR 514.106(b)(2)). This supplemental approval required a reevaluation of certain safety or effectiveness data in the application.

D. Patent Information

For current information on patents, see the Green Book Reports in the Animal Drugs @ FDA database.