Date of Approval: November 14, 2022

FREEDOM OF INFORMATION SUMMARY

APPLICATION FOR CONDITIONAL APPROVAL

Application number 141-567

PANOQUELL®-CA1

(fuzapladib sodium for injection)

Powder for Injection

Dogs

PANOQUELL®-CA1 is indicated for the management of clinical signs associated with acute onset of pancreatitis in dogs

Sponsored by:

Ishihara Sangyo Kaisha, Ltd.

Executive Summary

PANOQUELL®-CA1 (fuzapladib sodium for injection) is conditionally approved for the management of clinical signs associated with acute onset of pancreatitis in dogs.

An animal drug that addresses a serious or life-threatening disease, or addresses an unmet animal or human health need, for which demonstrating effectiveness would require a complex or particularly difficult study or studies is eligible for conditional approval. FDA determined that PANOQUELL®-CA1 was eligible for conditional approval under section 571(a)(1)(A)(ii) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) because it met these criteria.

Safety and Reasonable Expectation of Effectiveness

The sponsor conducted a pilot field study in client-owned dogs diagnosed with acute onset of pancreatitis. Enrolled dogs were of both sexes with a range of ages, weights, and breeds. The dogs had at least two clinical signs of acute onset of pancreatitis and a high (≥ 400 µg/L) canine pancreas-specific lipase value, measured by canine pancreatic lipase immunoreactivity (cPLI).

Dogs in the treatment group received fuzapladib sodium (not the final formulation of PANOQUELL®-CA1) once daily for 3 days by intravenous (IV) injection. Dogs in the control group were administered lyophilized excipients in sterile water by IV injection. The difference in group mean modified canine activity index (MCAI) scores between Day 0 and Day 3 was evaluated. The MCAI score includes seven areas of clinical relevance to dogs with acute onset of pancreatitis: activity, appetite, vomiting, cranial abdominal pain, dehydration, stool consistency, and blood in the stool.

On Day 3 of the study, the treatment group had an improved mean MCAI score compared to the control group. The mean change in MCAI score was greater for the treatment group than for the control group. The most common adverse reactions seen during the study were anorexia, digestive tract disorders, respiratory tract disorders, hepatopathy, and jaundice. Facial and tongue swelling, collapse, and seizure were reported voluntarily during post-approval monitoring of the drug in dogs in a foreign market. These adverse reactions occurred within 24 hours of drug administration.

The sponsor conducted a laboratory safety study in young, healthy, male and female Beagle dogs to evaluate the safety of PANOQUELL®-CA1 when administered IV at 0X, 1X, 3X, and 5X the labeled dose once daily for nine consecutive days (3X the labeled duration). The drug did not produce systemic toxicity and had an acceptable margin of safety. The administration of PANOQUELL®-CA1 resulted in swelling and bruising at the injection site, with associated gross pathology and histopathological findings; hypertension; and mild thrombocytopenia.

Conclusions

Based on the data submitted by the sponsor for the conditional approval of PANOQUELL®-CA1, FDA determined that the drug is safe and has a reasonable expectation of effectiveness when used according to the labeling.

Table of Contents

I. GENERAL INFORMATION

A. File Number

Application number 141567

B. Sponsor

Ishihara Sangyo Kaisha, Ltd.
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Drug Labeler Code: 064642

U.S. Agent Name and Address:
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C. Proprietary Name

PANOQUELL®-CA1

D. Drug Product Established Name

fuzapladib sodium for injection

E. Pharmacological Category

Leukocyte function-associated antigen 1 (LFA-1) activation inhibitor

F. Dosage Form

Powder for injection

G. Amount of Active Ingredient

4 mg fuzapladib sodium per mL

H. How Supplied

PANOQUELL®-CA1 consists of two separate vials. One vial contains 14 mg of fuzapladib sodium, 52.5 mg of mannitol, and 21 mg of tromethamine as sterile lyophilized powder. The second vial of 3.9 mL sterile diluent (bacteriostatic water for injection), containing 1.8% w/v benzyl alcohol, is for reconstituting the sterile lyophilized powder prior to use. No other diluent should be used.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

Prior to use, the sterile lyophilized powder should be reconstituted using 3.5 mL of the sterile diluent provided, resulting in a 4 mg/mL solution of PANOQUELL®-CA1. The reconstituted product is administered at a dosage of 0.4 mg (0.1 mL) per kg of body weight once daily for three consecutive days by intravenous bolus injection over 15 seconds to 1 minute.

K. Route of Administration

Intravenous injection

L. Species/Class

Dogs

M. Indication

PANOQUELL®-CA1 is indicated for the management of clinical signs associated with acute onset of pancreatitis in dogs.

II. EFFECTIVENESS

The conditional dose was selected based on two pilot studies. One of these pilot studies supports that fuzapladib sodium has a reasonable expectation of effectiveness when administered intravenously (IV) at a dosage of 0.4 mg/kg once daily for three days for the management of clinical signs associated with acute onset of pancreatitis in dogs.

Conditional Dose: The conditional dose for the indication, "for the management of clinical signs associated with acute onset of pancreatitis in dogs", is 0.4 mg/kg IV once daily for three days. The safety data and the data to demonstrate reasonable expectation of effectiveness provide support for this conditional dose.

A. Dosage Characterization

The dose of PANOQUELL®-CA1 administered IV at 0.4 mg/kg once daily for three days is supported by two pilot studies. During development, fuzapladib sodium was also referred to as IKV-741.

1. Study Title: IKV-741 Dose Determination Study-A Study on a Canine Pancreatitis Model. (Study No. AH0019)

   A placebo-controlled laboratory study was conducted to determine the clinical dose of fuzapladib sodium. In an experimentally-induced canine pancreatitis model resulting from retrograde infusion of bile acids into the pancreatic duct, fuzapladib sodium (not commercial formulation) was administered IV at 0 (n = 5), 0.04 (n = 3), 0.4 (n = 5), or 4.0 (n = 2) mg/kg bodyweight for three days. Therapeutic effects were observed in both the 0.4 and 4.0 mg/kg groups, while the 0.04 mg/kg group showed reduced effectiveness compared to the two higher dosages. Based on the results of the study, 0.4 mg/kg was selected as the lowest effective dose.

2. Study Title: A Pilot, Randomized, Blinded, Placebo-Controlled Dose Ranging Clinical Field Study to Evaluate the Effectiveness and Safety of IKV-741 for the Treatment of Acute Pancreatitis in Client-Owned Dogs. (Study No. AH0027)

   Refer to the Reasonable Expectation of Effectiveness section for more information.

B. Reasonable Expectation of Effectiveness

1. Pilot Field Effectiveness Study

   Title: A Pilot, Randomized, Blinded, Placebo-Controlled Dose Ranging Clinical Field Study to Evaluate the Effectiveness and Safety of IKV-741 for the Treatment of Acute Pancreatitis in Client-Owned Dogs. (Study No. AH0027)

   Study Dates: July 4, 2017 to September 23, 2019

   Study Locations:
   Sacramento, CA
   Wheat Ridge, CO
   New Preston, CT
   Buffalo Grove, IL
   Fort Wayne, IN
   Franklin, IN
   Catonsville, MD
   Springfield, MO
   Worthington, OH
   Quakertown, PA
   Farragut, TN

   Study Design: This was a pilot, randomized, blinded, vehicle-controlled, dose ranging clinical field study in client-owned dogs diagnosed with acute onset of pancreatitis.

   Objective: The study was designed to evaluate the safety and effectiveness of fuzapladib sodium to manage clinical signs associated with acute onset of pancreatitis when administered IV at 0.4 mg/kg body weight once daily for three days.

   Study Animals: A total of 61 dogs (34 females; 28 males) diagnosed with acute onset of pancreatitis were enrolled. Thirty-six evaluable cases completed the study (17 in the fuzapladib sodium group and 19 in the vehicle control group). The enrolled dogs were 1.8 to 15.9 years of age with initial body weights between 3.1 to 44.9 kg and were of various breeds, including mixed breed.

   Experimental Design: Dogs were randomly assigned to treatment groups based on their order of enrollment into the study using randomization tables generated by the statistician. Each site had a unique randomization schedule. Investigators and examining veterinarians were masked to treatment group

assignments. Dispensing staff were not masked to treatment group and did not participate in clinical assessments. The study was conducted in accordance with Good Clinical Practice principles.

Table II.1. Treatment Groups

Treatment Group	Number of Enrolled Dogs	Dose
Vehicle Control (lyophilized excipients)[a]	30	0.1 mL/kg administered IV once daily for 3 days
Fuzapladib sodium	31	0.4 mg/kg administered IV once daily for 3 days

[a] D-Mannnitol and tromethamine

Inclusion Criteria:
- Male and female client-owned dogs, mixed and purebred, ≥ 6 months of age on Day 0.
- Presence of at least two clinical signs associated with acute onset of pancreatitis: vomiting, anorexia, abdominal pain, depression, diarrhea, dehydration.
- Day 0 abnormal SNAP® canine pancreas-specific lipase (cPL)™ result and/or Spec cPL® value ≥ 400 µg/L (IDEXX Laboratories, Westbrook ME). Eligibility was confirmed by clinical pathology results and canine pancreatic lipase immunoreactivity (cPLI) concentrations of ≥ 400 µg/L from the sample collected on Day 0.
- Owner reviewed and signed informed consent.

Exclusion Criteria:
- Presence of gastrointestinal obstruction/foreign body, abdominal mass, or severe concurrent life-threatening illness other than acute pancreatitis (e.g., severe cardiopulmonary disease, liver failure, end-stage renal disease, metabolic disease, autoimmune disorders, severe anemia, systemic infection, and neoplasia).
- Presence of any condition that in the opinion of the Investigator would interfere with treatment administration and/or assessment of effectiveness.
- Serious life-threatening pancreatitis.
- Use of any of the following concomitant therapies within one week prior to enrollment: short-acting corticosteroids, non-steroidal anti-inflammatory drugs (NSAID), immunosuppressants, anti-cancer drugs, herbal/homeopathic remedies, and whole blood transfusions.
- Use of long-acting corticosteroids within 8 weeks prior to enrollment.
- Dogs intended for breeding or lactating, pregnant, or in estrus.
- Dogs with clinical pathology findings considered abnormal, clinically significant, and/or potentially influencing the study outcome, apart from findings consistent with acute pancreatitis or previously identified stable chronic conditions.
- Dogs displaying a temperament that interfered with administration of the test article, evaluation of clinical signs, or collection of blood samples by the hospital.

- Dogs enrolled in other studies within the previous three weeks prior to screening or currently being administered other experimental or investigational therapies.
- Dogs owned by the Investigator/examining veterinarian, clinic staff, or their direct relatives.

Drug Administration: Dogs assigned to the fuzapladib sodium treatment group received fuzapladib sodium (non-final formulation) at a dose of 0.4 mg/kg once daily for three days by IV bolus injection (administered over 15 sec to 1 min). Prior to use at the veterinary hospital, the lyophilized powder was solubilized in 1 mL of Sterile Water for Injection, USP, resulting in a 4 mg/mL solution of fuzapladib sodium equivalent per vial. The vehicle control group received excipient lyophilized powder solubilized in 1 mL of Sterile Water for Injection, USP. All doses were administered at a rate of 0.1 mL/kg body weight/day for three days.

All dogs enrolled in the study received the standard of care for acute onset of pancreatitis, including fluids, nutritional support, pain medications (excluding non-steroidal anti-inflammatory drugs), anti-emetics, and medications used to treat well-controlled pre-existing conditions. Some dogs also received parasiticides and vaccinations.

Measurements and Observations:
- Physical examinations were performed once daily on each day of the study and, when possible, on early withdrawal from the study.
- C-reactive protein (CRP), cPLI (as measured by Spec cPL®), and Meso Scale Discovery/Multiplex Cytokine Assay (MSD/MCA) cytokine assays were performed once daily on each day of the study and, when possible, on early withdrawal from the study.
- Samples for hematology, serum chemistry, and urinalysis were collected on Day 0 and at completion of the study.
- SNAP® cPL™ testing was performed on Day 0.
- The Canine Acute Pancreatitis Clinical Severity Index (CAPCSI)[1] score was performed daily and included four areas of clinical relevance to dogs with acute onset of pancreatitis: cardiac, respiratory, intestinal integrity, and vascular forces.
- The sponsor-generated Modified Canine Activity Index (MCAI) score was performed daily. The MCAI evaluated seven clinical signs relevant in dogs with acute pancreatitis, and scored each based on the following:

    - Activity
      0 = Normal (as usual)
      1 = Slightly decreased (the animal stands less than usual)
      2 = Moderately decreased (the animal is reluctant to stand up)
      3 = Severely decreased (the animal cannot stand up)

    - Appetite (voluntary food intake)
      0 = Normal (the animal ate more than ¾ of the food)

[1] Mansfield CS, James FE, Robertson ID. Development of a clinical severity index for dogs with acute pancreatitis. *J Am Vet Med Assoc*. 2008 Sep 15;233(6):936-44.

1 = Slightly decreased (the animal ate about ½ of the food)
2 = Moderately decreased (the animal ate about ¼ of the food)
3 = Severely decreased (the animal did not eat much of the food or at all)

- Vomiting
  0 = None
  1 = 1 - 2 times/day
  2 = 3 - 4 times/day
  3 = ≥ 5 times/day

- Cranial abdominal pain
  0 = None (no signs of pain)
  1 = Mild (abdominal wall resistance or other signs of pain are elicited upon palpation of the abdomen, the animal moves slowly or is less responsive)
  2 = Moderate (the animal resists palpation, is reluctant to move when encouraged, does not lie on its side)
  3 = Severe (persistent vocalization, howling and/or insomnia)

- Dehydration
  0 = None (< 5%, no signs of dehydration)
  1 = Mild (5%, slight loss of skin elasticity)
  2 = Moderate (6 - 8%, decreased skin turgor, slight delayed capillary refill time, dry mucous membranes, sunken eyes)
  3 = Severe (≥ 10%, severely decreased skin turgor, delayed capillary refill time, deeply sunken eyes, severely dry mucous membranes)

- Stool consistency
  0 = Normal (well formed)
  1 = Soft (slightly watery and poorly formed)
  2 = Diarrhea (no form and runny)
  3 = Watery (watery with no solids and pale)

- Blood in the stool
  0 = Absent
  1 = Present

The primary effectiveness variable was the change in group mean total MCAI score from Day 0 (pre-treatment) to Day 3, as assessed by the investigator.

Statistical Methods: Each dog served as the experimental unit. The total MCAI scores were assessed by repeated measures analysis of covariance. The model included fixed effects of group, day, and group-by-day interaction with the Day 0 value as a covariate. Site and group-by-site interaction were included as random effects. The covariance structure that provided the smallest Akaike Information Criterion value was used. Covariance structures tested include Compound Symmetry (CS), heterogeneous CS, first-order autoregressive, and heterogenous autoregressive. All analyses were performed using Statistical Analysis System (SAS/STAT® software, Version

9.4, SAS Institute Inc., Cary, NC, USA). All hypotheses were tested at a two-sided 0.05 level of significance, where appropriate.

Results: Effectiveness was evaluated in 36 dogs (17 in the fuzapladib sodium group and 19 in the vehicle control group). Of the 25 dogs excluded from the effectiveness analysis, most of these dogs (19) began the study before the cPLI results from Day 0 were finalized and were later excluded because their cPLI results were ≤ 400 µg/L. Six dogs were excluded for other reasons.

Day 0 mean MCAI scores for the fuzapladib sodium and vehicle control groups were 8.53 and 7.68, respectively. The changes in the mean total MCAI scores from Day 0 to 3 for the fuzapladib sodium and vehicle controls groups were -7.7 and -5.7, respectively. Dogs treated with fuzapladib sodium had a statistically significant reduction in MCAI scores compared to control (p = 0.0193). See Table II.2 below.

Table II.2. MCAI Total Score Change from Day 0 to Day 3

Group	**Fuzapladib sodium**	**Vehicle Control**
Number of Dogs	17	19
Mean Change in MCAI Score[a]	-7.7	-5.7
Standard Deviation	2.54	3.79
Median Change in MCAI Score	-7.0	-6.0
Minimum, Maximum Change in MCAI Score	-4, -14	1, -10

[a] Dogs treated with fuzapladib sodium had a statistically significant reduction in MCAI scores compared to control (p = 0.0193)

Adverse Reactions: Field safety was evaluated in 31 dogs treated with fuzapladib sodium and 30 dogs receiving vehicle control. The most common adverse reactions were anorexia, digestive tract disorders, respiratory tract disorders, and hepatopathy and jaundice. The adverse reactions observed in the study and the number of dogs experiencing each adverse reaction are summarized in Table II.3 below.

Table II.3. Adverse Reactions During the Pilot Field Study

Adverse Reaction	**Fuzapladib sodium n = 31 (%)**	**Vehicle Control n = 30 (%)**
Anorexia	5 (16.1%)	2 (6.7%)
Digestive tract disorders	5 (16.1%)	3 (10.0%)
Respiratory tract disorders	4 (12.9%)	3 (10.0%)
Hepatopathy, jaundice	4 (12.9%)	2 (6.7%)
Abnormal urine	3 (9.7%)	2 (6.7%)
Diarrhea	3 (9.7%)	1 (3.3%)
Arrhythmia	2 (6.5%)	1 (3.3%)
Cardiac arrest	2 (6.5%)	0
Hyperthermia	2 (6.5%)	0

Adverse Reaction	Fuzapladib sodium n = 31 (%)	Vehicle Control n = 30 (%)
Pruritis, urticaria	2 (6.5%)	0
Hypersalivation	2 (6.5%)	0
Heart murmur	1 (3.2%)	2 (6.7%)
Limb edema	1 (3.2%)	2 (6.7%)
Subcutaneous swelling, bruising at injection site	1 (3.2%)	1 (3.3%)
Tremor/shivering/shaking	1 (3.2%)	1 (3.3%)
Abrasion	1 (3.2%)	1 (3.3%)
Cerebral edema	1 (3.2%)	0
Anaphylaxis	1 (3.2%)	0
Hypertension	1 (3.2%)	0

In Table II.3, digestive tract disorders included regurgitation (1 fuzapladib, 2 vehicle control), vomiting (1 fuzapladib, 1 vehicle control), flatulence (1 fuzapladib), nausea (1 fuzapladib), and enteritis (1 fuzapladib). Respiratory tract disorders included pneumonia (2 fuzapladib, 1 vehicle control), inspiratory crackles (1 fuzapladib, 2 vehicle control), tachypnea (2 fuzapladib), and dyspnea (1 fuzapladib). Abnormal urine included proteinuria (2 fuzapladib, 2 vehicle control), hematuria (2 vehicle control), and malodorous urine (1 fuzapladib). Some of these dogs were reported with more than one abnormality.

Note: Some dogs were reported with an adverse reaction on more than one occasion, but are only presented once in the table above for each reported adverse reaction.

Five out of the 61 enrolled dogs died during the study: four in the fuzapladib sodium group and one in the vehicle control group. Two additional dogs in the vehicle control group were euthanized shortly after completion of the study. Of the seven dogs that died or were euthanized during or after the study, three deaths could be attributed to complications from severe acute onset of pancreatitis: two in the fuzapladib sodium group and one in the vehicle control group. One dog in the fuzapladib sodium group was suspected to have aspiration pneumonia and died after experiencing cardiac arrest. One dog in the vehicle control group was euthanized because of a poor prognosis. Two deaths could be attributed to causes other than acute onset of pancreatitis: one dog in the fuzapladib sodium group had intestinal lymphoma and one vehicle control group dog had a cranial thromboembolic event and a pheochromocytoma.

Foreign Market Experience
The following adverse events were reported voluntarily during post-approval use of the product in dogs in foreign markets: facial and tongue swelling, collapse, and seizure. These adverse events occurred within 24 hours of administration.

Conclusions: The study results support a reasonable expectation of effectiveness for the use of PANOQUELL®-CA1 administered IV at the conditional dose of 0.4 mg/kg once daily for three days for the management of clinical signs associated with acute onset of pancreatitis in dogs.

III. TARGET ANIMAL SAFETY

A. Laboratory Margin of Safety Study

Title: Target Animal Safety of Fuzapladib in Beagle Dogs. (Study No. AH0186)

Study Dates: March 19, 2021 to November 30, 2021

Study Location: Ontario, Canada

Study Design:

Objective: To evaluate the margin of safety of PANOQUELL®-CA1 when administered IV to Beagle dogs at doses of 0 mg/kg (0X), 0.4 mg/kg (1X), 1.2 mg/kg (3X), and 2 mg/kg (5X) once daily for nine consecutive days.

Study Animals: The study included 32 intact Beagle dogs (16 males and 16 females), aged approximately 6.5 - 7.5 months old, with a bodyweight range of 5.8 - 8.7 kg at the start of dosing. Dogs included in the study were determined to be healthy based on physical examination and clinical pathology findings.

Experimental Design: The dogs were randomly allocated to one of four sex-balanced dose groups of eight dogs each. Dogs were further allocated to one of two cohorts of 16 dogs each (cohorts 1 and 2) to accommodate the logistical needs of the test facility. All study personnel conducting clinical observations were masked to treatment assignment. The study was conducted in accordance with Good Laboratory Practice (GLP) regulations.

Table III.1. Treatment Groups

Group	Number and Sex of Dogs	Test Article	Dose (mg/kg)	Dose Volume (mL/kg)
0X (control)	4 males/4 females	Saline	0	0.5
1X	4 males/4 females	Fuzapladib sodium	0.4	0.1
3X	4 males/4 females	Fuzapladib sodium	1.2	0.3
5X	4 males/4 females	Fuzapladib sodium	2	0.5

Drug Administration: After acclimation, dogs in cohorts 1 and 2 were dosed IV once daily for nine consecutive days. As cohort 1 started the treatment phase two days prior to cohort 2, the first day of dosing was Day 14 for cohort 1 and Day 16 for cohort 2. Dogs were dosed according to pen order, and all subsequent doses were administered at 24-hour (± 1 hour) intervals. The injection site (either cephalic or lateral saphenous) was clipped and cleaned. A butterfly

needle or indwelling catheter was used to inject either the test or control article. Approximately 1 mL of flush was injected to clear the line of any remaining article prior to the removal of the butterfly needle or indwelling catheter.

Measurements and Observations:

- Clinical observations: conducted twice daily, and non-scheduled observations as needed.
- Physical examinations: three times during acclimation and on Days 14, 17, and 22 (cohort 1) and 16, 19, and 24 (cohort 2).
- Body weight: three times during acclimation and on Days 16, 19, and 22 (cohort 1) and 15, 18, 21, and 24 (cohort 2).
- Food consumption: beginning on Day -14, the daily amount of food offered and remaining was weighed and recorded once daily.
- Injection site evaluations: once coinciding with the first daily clinical observation (prior to daily dosing), once at 2 hours (±1 hour) post-dosing, and once coinciding with the second daily clinical observation.
- Hematology, clinical chemistry, and coagulation evaluations: three times during acclimation and on Days 15 and 22 (cohort 1), and Days 17 and 24 (cohort 2).
- Urinalysis: twice during acclimation and on Days 15 or 16 and 22 or 23 (cohort 1), and Days 17 or 18 and 24 or 25 (cohort 2.)
- Electrocardiography: once during acclimation, and post-dosing on Days 15 and 20 (cohort 1), and Days 17 and 22 (cohort 2).
- Non-invasive systolic blood pressure monitoring: twice during acclimation and post-dosing on Days 16 and 21 (cohort 1), and Days 18 and 23 (cohort 2)
- Gross necropsy: dogs were euthanized for necropsy procedures on either Day 23 (cohort 1) or Day 25 (cohort 2).
- Histopathology: protocol-specified tissues were processed to slides, stained, and microscopically evaluated.
- Plasma fuzapladib sodium levels (toxicokinetic analysis): Blood samples were obtained after the first and ninth dose at pre-dose, and 5 min, 30 min, 1 hour, 3 hours, 7 hours, and 12 hours post-dose. Blood samples were also obtained 24 hours post-dose after the first, second, third, and eighth dose prior to dosing.

Pain on injection was evaluated during test or control article administration using the following scale:

- 0: no pain (dog appeared unaffected)
- 1: mild pain (dog made an attempt to retract the affected limb)
- 2: moderate pain (dog vocalized and/or vigorously tried to retract the affected limb)
- 3: marked pain (dog vocalized loudly, attempted to evade restraint, and/or became aggressive)

Injection site observations were recorded using the following scoring system:
Swelling:

- 0: No swelling
- 1: Mild swelling
- 2: Moderate swelling
- 3: Marked swelling

Erythema:

- 0: No erythema
- 1: Mild erythema
- 2: Moderate erythema
- 3: Marked erythema

Pain:

- 0: No pain on palpation
- 1: Mild pain on palpation
- 2: Moderate pain on palpation
- 3: Marked pain on palpation

Statistical Methods: The unit of observation and statistical analysis was the individual dog. For continuous outcomes measured only once during the study (absolute organ weights and organ weight relative to body weight), analysis of variance (ANOVA, using the MIXED procedure in SAS, SAS Institute, Cary, NC; version 9.4) was used to evaluate a model containing dose, sex, and the sex-by-dose interaction as fixed effects.

If the dose-by-sex interaction was significant at the 10% level, within-sex dose effects were evaluated using pair-wise comparisons of each dose group against control using linear contrasts at an unadjusted alpha = 0.10. If the dose-by-sex interaction was not significant, the main effect of dose was evaluated at alpha = 0.10. If this term was significant, pair-wise comparisons of each dose group against control using linear contrasts at an unadjusted alpha = 0.10 were performed. Organ weight data were expressed as absolute values as well as a percent of the final body weight.

Continuous variables measured at multiple times during the study (including heart rate, respiratory rate, rectal temperature, body weight, blood pressure, food consumption, clinical chemistry, hematology, coagulation, and urine specific gravity) were analyzed by a repeated measures analysis of covariance (RMANCOVA) model, with dose, sex, time, dose-by-sex, sex-by-time, dose-by-time, and dose-by-sex-by-time terms as fixed effects in the model, and animal identified as the subject in the repeated statement (the MIXED procedure in SAS, RMANCOVA). Pre-dose values were used as a covariate and remained in the model regardless of statistical significance. If multiple pre-dose values were provided (i.e., body weight), the values nearest to the first day of dosing were used as the covariate. For food consumption, daily mean intake values obtained from the week prior to Day 14 were included as the covariate.

For variables measured at equal intervals, the covariance structure in the repeated measures analysis was investigated using four structural assumptions, namely, compound symmetry (CS), heterogenous compound symmetry (CSH), autoregressive(1) [AR(1)], and heterogenous autoregressive(1) [ARH(1)]. For variables measured at unequal intervals, the covariance structure in the repeated measures analysis was investigated using three structural assumptions; namely CS, CSH, and spatial power [SP(POW)]. The assumption giving the minimum value of the Akaike Information Criterion (AIC) was selected in the final analysis.

A representative variable within an outcome class (calcium values for clinical chemistry, hemoglobin for hematology, activated partial thromboplastin time for coagulation) was used in the assessment of the covariance structure. The

structure appropriate for this particular variable was used for the remaining variables within that outcome class.

The dose-by-sex-by-time interaction was evaluated at the 5% level. If the dose-by-sex-by-time interaction was significant (alpha = 0.05), summary statistics for each dose group at each time point within each sex was provided. No further hypothesis testing was conducted. If the dose-by-sex-by-time interaction was not significant, then the two-way interactions of dose-by-sex and dose-by-time were evaluated. If the dose-by-sex interaction was significant at the 10% level, within-sex dose effects were evaluated using pair-wise comparisons of each dose group against control using linear contrasts at an unadjusted alpha = 0.10. If the dose-by-time interaction was significant at the 10% level (regardless of the significance of the dose-by-sex term), then pair-wise comparisons of each dose group against control for each time point using linear contrasts at an unadjusted alpha = 0.10 was performed.

If neither of the two-way interactions involving dose were significant, then the main effect of dose group was evaluated at the 10% level. If the dose effect was significant, then pair-wise comparisons of each dose group against control using linear contrasts at an unadjusted alpha = 0.10 was performed.

Differences in plasma fuzapladib sodium concentrations for the dose groups following the first and ninth dose was assessed by ANOVA on the calculated area under the curve (AUC). Time points included in the calculation of the AUC were prior to dosing and 5 min, 30 min, 1 hr, 3 hr, 7 hr, 12 hr and 24 hr post dose. For each dog, the AUC0-tlast (AUC from time zero to the last quantifiable concentration) was calculated using the linear trapezoidal method. The AUC values were natural log-transformed prior to statistical analysis. Results from the first and ninth dose were evaluated separately using the statistical model and approach described above for continuous variables, measured once.

Results: Mortality and Morbidity: All dogs survived to study termination and no clinically relevant morbidity was observed during the study.

Body weight and Food consumption: There were no test article-related related findings on body weight and food consumption.

Clinical observations and physical examinations: Hypersalivation was reported in one control dog and two 5X dogs.

Injection Site Evaluations: Dosing was generally well tolerated. There was one incidence of a pain score of 2 documented in one dog in the 5X group during the final dose administration. This pain score was deemed to be associated with the pain from repeated IV catheterization rather than test article administration. There were no abnormal scores documented for injection site pain occurring after injections.

Swelling was commonly documented in all dose groups, including the control group. The frequency increased for all groups as number of injections increased. The frequency and severity of swelling increased in the 5X group compared to the other groups. A score of moderate was observed in two dogs in the 5X group.

Mild erythema at injection sites was documented at comparable frequencies among all groups and time points post-injection. Moderate erythema was observed in six dogs (two dogs in the control group, one dog in the 3X group, and three dogs in the 5X group) throughout the study. Erythema was considered procedure related and not associated with the test article administration.

Bruising was observed in all groups, including the control. However, bruising occurred more frequently in the 3X and 5X groups.

Electrocardiograms (ECG): There were no rhythm or conduction abnormalities observed in any dog.

Blood Pressure: There was a statistically significant difference in systolic blood pressure values between the 5X group and the control group ($p = 0.068$), with the 5X group having numerically higher values. Mean systolic blood pressure values in the 5X group were statistically significantly different between the 5X group and the control group, with the 5X group having a numerically higher mean value ($p = 0.100$). Systolic blood pressure values remained relatively consistent throughout the duration of the study for all dose groups, including the controls, with the exception of the last day (Day 21 for cohort 1 and Day 23 for cohort 2). When using a threshold of ≥ 160 mmHg to define hypertension, only dogs administered fuzapladib sodium exhibited hypertension. Hypertension, with values ranging from 163 - 194 mmHg, occurred in one dog in the 1X group, one dog in the 3X group, and four dogs in the 5X group.

Hematology: The dose-by-time interaction was statistically significant for percent hematocrit (HCT) ($p = 0.088$) and platelet values ($p = 0.058$). However, within day, comparisons between dose groups to controls were not significant for either analyte. One 5X dog had decreased HCT and hemoglobin values that started in acclimation and continued to decrease throughout the study. This dog did not exhibit any abnormal clinical signs.

Mild thrombocytopenia (between 121 - 169 x 10^3/L; reference range: 171- 361 x 10^3/L) was observed in two 1X dogs, one 3X dog, and one 5X dog during the treatment phase of the study on one day each. The 3X dog was also reported to have platelet clumping on the smear at the same time the thrombocytopenia was reported. One 1X dog was noted to have bruising on Day 15, which coincided with the finding of thrombocytopenia. However, this dog's platelet values remained within the reference range for the rest of the study. The thrombocytopenia noted in the other 1X dog was observed on the last study day. While this dog's platelet values were within the reference range on all previous days, the platelet values trended downward as the study progressed.

Clinical Chemistry: One 5X dog had a mildly decreased potassium value of 4.06 mmol/L (reference range: 4.08 - 4.83 mmol/L) on Day 17, which resolved by the end of the study.

On Day 22, one 5X dog had elevations in aspartate aminotransferase (AST) of 69.63 U/L (reference range: 19.35 - 49.51 U/L), alkaline phosphatase (ALP) of 117.59 U/L (reference range: 27.23 - 115.35 U/L), and creatinine kinase (CK) of 1492.15 U/L (reference range: 84.29 - 444.27 U/L). The alanine

aminotransferase (ALT) value on Day 22 was 58.9 U/L (reference range: 21.02 - 62.61 U/L). While ALT values were within the reference range prior to Day 22, they were noted to be steadily increasing. This dog had both swelling and bruising reported at the injection site and was reported to be difficult with handling.

Coagulation/Urinalysis: There were no clinically relevant findings for coagulation values or urinalysis.

Necropsy Examination: Gross pathology revealed focal subcutaneous hemorrhage of individual injection sites. Injection site severity scores were calculated based on the diameter, grade during necropsy, and number. The groups administered fuzapladib sodium had a dose-dependent greater severity score compared to the control group.

The following microscopic observations were noted in dogs in the 1X, 3X, and 5X groups: dermal fibroplasia and subcutaneous inflammation, dermal inflammation, and subcutaneous hemorrhage at the cephalic vein injection sites. These findings did not occur in the dogs in the control group.

Organ Weights: There were no clinically relevant test article related changes found.

Toxicokinetics: Plasma concentrations of fuzapladib sodium were measured using a validated High Performance Liquid Chromatography–Mass Spectrometry (HPLC-MS/MS) bioanalytical method. Minimal accumulation was observed with a mean accumulation ratio of 1.37, 1.36, and 1.35, for the 0.4, 1.2, and 2 mg/kg dose groups, respectively. The extent of plasma exposure (AUC) was greater than dose-proportional between 0.4 and 2 mg/kg after the first dose and ninth dose. Calculated pharmacokinetic (PK) values are provided in Table III.2.

Table III.2. Mean ± standard deviation (SD) pharmacokinetic parameters of fuzapladib sodium following nine IV doses of 0.4 mg/kg in dogs

Parameter	Mean ± SD
C_0 (µg/mL)	3.55 ± 1.17
AUC_{ss} (hour*µg/mL)	19.2 ± 12.7
$T_{1/2}$ (hour)	7.32 ± 4.08
V_{ss} (L/kg)	0.216 ± 0.070
Cl_{ss} (L/h/kg)	0.026 ± 0.009

C_0: Back-extrapolated plasma concentration of fuzapladib sodium at time zero by a log-linear regression of first two data points following IV administration
AUC_{ss}: Area under the plasma concentration versus time curve during dosing interval at steady state
$T_{1/2}$: Terminal elimination half-life
V_{ss}: Volume of distribution at steady state
Cl_{ss}: Clearance at steady state

Conclusions: The administration of PANOQUELL®-CA1 as an IV injection once daily for nine days at doses of 0, 0.4, 1.2, and 2 mg/kg fuzapladib sodium did not produce systemic toxicity and had an acceptable margin of safety. The

administration of PANOQUELL®-CA1 resulted in swelling and bruising at the injection site, with associated gross pathology and histopathological findings, hypertension, and mild thrombocytopenia. This nine-day safety study supports the safe use of PANOQUELL®-CA1 when administered IV to dogs, according to the label.

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, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for conditional approval of this application.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to PANOQUELL®-CA1:

Not for use in humans. Keep this medication out of reach of children.

In case of accidental self-injection:

- Seek medical advice immediately and show the package insert or label to the physician.

In case of accidental skin contact:

- Wash the exposed skin with water for at least 15 minutes.
- If redness and swelling occur, seek medical advice immediately and show the package insert or label to the physician.

In case of accidental eye exposure:

- Wash the eyes with water for at least 15 minutes.
- If wearing contact lenses, rinse the eyes first, then remove contacts and continue to rinse with water.
- If redness and swelling occur, seek medical advice immediately and show the package insert or label to the physician.

In case of accidental ingestion:

- Rinse the mouth out with water.
- Do not induce vomiting unless directed to do so by medical personnel.
- Seek medical advice immediately and show the package insert or label to the physician.

Limited data is available on the potential teratogenic effects of fuzapladib. Therefore, anyone who is pregnant, breast feeding, or planning to become pregnant should avoid direct contact with PANOQUELL®-CA1.

Anyone with known hypersensitivity to fuzapladib or to any of the excipients should avoid contact with PANOQUELL®-CA1.

VI. AGENCY CONCLUSIONS

The data submitted in support of this application satisfy the requirements of section 571(b) of the FD&C Act. The data demonstrate that PANOQUELL®-CA1, when used according to the label, is safe and has a reasonable expectation of effectiveness for the management of clinical signs associated with acute onset of pancreatitis in dogs.

A. Conditional Approval Eligibility

In 2018, the legislation reauthorizing FDA's animal drug user fee program (Animal Drug User Fee Program, or ADUFA, IV) expanded the conditional approval pathway to allow certain additional new animal drugs that are not Minor Use/Minor Species (MUMS) drugs to be eligible for conditional approval. As provided in section 571(a)(1)(A)(ii) of the FD&C Act, as amended by ADUFA IV, to qualify for conditional approval, the non-MUMS new animal drug must meet the following two criteria:

1. The new animal drug is intended to treat a serious or life-threatening disease or condition OR addresses an unmet animal or human health need; AND

2. A demonstration of effectiveness would require a complex or particularly difficult study or studies.

PANOQUELL®-CA1 was determined to be eligible for conditional approval under these provisions because it controls a serious or life-threatening disease or condition, addresses an unmet animal health need, and the demonstration of effectiveness requires a complex or particularly difficult study or studies. The condition, acute onset of pancreatitis in dogs, is a disease or condition associated with mortality and morbidity that has substantial impact on day-to-day functioning in the target animal. Therefore, the conditionally approved use addresses a serious or life-threatening disease or condition. The management of clinical signs associated with acute onset of pancreatitis in dogs was also determined to be an unmet animal health need because there is no approved animal drug currently being marketed in the United States for this use in dogs. Finally, based on the difficulty in diagnosing the disease, it was determined that the demonstration of effectiveness requires a complex or particularly difficult study or studies.

B. Marketing Status

PANOQUELL®-CA1 is conditionally approved for one year from the date of approval and is annually renewable for up to four additional one-year terms.

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 properly diagnose clinical signs associated with acute onset of pancreatitis, properly administer the injection, and properly monitor the safe use of the product, including treatment of any adverse reactions.

C. Exclusive Marketing Rights

PANOQUELL®-CA1, as approved in our approval letter, does not qualify for exclusive marketing rights under section 573(c) of the FD&C Act because it is not a designated new animal drug under section 573(a) of the FD&C Act.

D. Patent Information

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