Date of Approval: May 10, 2024

FREEDOM OF INFORMATION SUMMARY

APPLICATION FOR CONDITIONAL APPROVAL

Application number 141-577

UpCard®-CA1

(torsemide oral solution)

Dogs

UpCard®-CA1 is indicated for use with concurrent therapy with pimobendan, spironolactone, and an angiotensin converting enzyme (ACE) inhibitor for the management of pulmonary edema in dogs with congestive heart failure caused by myxomatous mitral valve disease (MMVD).

Sponsored by:

Vetoquinol USA, Inc.

Executive Summary

UpCard®-CA1 (torsemide oral solution) is conditionally approved for use with concurrent therapy with pimobendan, spironolactone, and an angiotensin converting enzyme (ACE) inhibitor for the management of pulmonary edema in dogs with congestive heart failure caused by myxomatous mitral valve disease (MMVD). The drug is a loop diuretic that is given orally once daily.

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 expanded conditional approval. Congestive heart failure caused by MMVD is a serious and life-threatening disease in dogs because it is fatal when not treated. Due to the nature of the disease, it would be time consuming and difficult to enroll sufficient numbers of eligible dogs in effectiveness studies. Additionally, diagnosis of the disease requires advanced and complicated tests. Therefore, the Food and Drug Administration (FDA) determined that UpCard®-CA1 met the eligibility criteria for expanded conditional approval.

Safety and Reasonable Expectation of Effectiveness

The sponsor conducted a field study in client-owned dogs comparing the effectiveness of torsemide tablets to another loop diuretic (furosemide) to manage pulmonary edema secondary to congestive heart failure caused by MMVD. Enrolled dogs were of both sexes with a range of ages and weights; however, most were older, small-breed dogs. The dogs were diagnosed with class II, III, or IV heart failure based on the modified New York Heart Association (NYHA) scoring system and had experienced at least one episode of pulmonary edema due to their heart failure. A dog with modified NYHA class II heart failure has clinical signs (fatigue, dyspnea, cough) during intense or extended exercise; a dog with class III has clinical signs during moderate exercise; and a dog with class IV has complete exercise intolerance and clinical signs at rest. Dogs were allowed to continue on standard of care therapy for congestive heart failure if treatment was started before enrollment, which included ACE inhibitors, pimobendan, digoxin, calcium channel blockers, and beta blockers.

Dogs diagnosed with MMVD that were clinically stable and had received furosemide tablets for at least 10 days prior to Day 0 were included in the analysis for reasonable expectation of effectiveness. Starting on Day 0, dogs either continued with twice daily furosemide tablets or were transitioned to torsemide tablets once daily. The primary criterion for effectiveness was response rate to treatment on Day 84. A dog was considered to have a successful response if the dog remained clinically stable and pulmonary edema had not increased compared to Day 0. The response rate on Day 84 was slightly higher for dogs in the torsemide group compared to dogs in the furosemide group. Therefore, torsemide tablets were non-inferior to (not worse than) furosemide tablets at managing pulmonary edema of cardiac origin in dogs with MMVD. More adverse events were reported in dogs in the torsemide group compared to dogs in the furosemide group. The most common adverse events associated with torsemide were polyuria/polydipsia, renal insufficiency (including increased blood urine nitrogen (BUN) and serum creatinine and renal failure), urinary incontinence, and electrolyte disturbances, including hypokalemia, hypochloremia, hypercalcemia, and hypomagnesemia.

The sponsor conducted a pharmacokinetic bridging study in healthy male and female beagles to determine the relative bioavailability of UpCard®-CA1 compared to torsemide tablets. Fasted dogs received one oral dose of either UpCard®-CA1 or torsemide tablets, followed by a washout period of 14 days, and then received the opposite drug from the first dose. Blood and urine samples were taken multiple times after each dose. The relative bioavailability of UpCard®-CA1 in plasma and urine was high, and therefore, both formulations (the oral solution and the oral tablets) are expected to have similar diuretic activity and safety profiles. Additionally, administration of torsemide as an oral solution formulation will allow for more precise dose adjustments than with tablets.

The sponsor conducted two laboratory studies to support the safety of UpCard®-CA1. In the six-month margin of safety study, UpCard®-CA1 was given orally once daily to young, healthy, male and female beagles at 0X, 0.25X (0.11 mg/kg), 1X (0.44 mg/kg), and 1.5X (0.66 mg/kg) the maximum conditionally approved dose. The drug was well-tolerated in all treatment groups. Because loop diuretics have a well-characterized safety profile and can cause serious adverse events at high doses, the safety of UpCard®-CA1 was evaluated using doses lower than the generally recommended 1X, 3X, and 5X treatment groups.

In the 13-week margin of safety study, torsemide tablets were given orally once daily to young, healthy, male and female beagles at 0X, 0.23X (0.1 mg/kg), 0.68X (0.3 mg/kg), and 1.36X (0.6 mg/kg) the maximum conditionally approved dose. The results showed that torsemide has an adequate margin of safety for managing pulmonary edema related to congestive heart failure in dogs with MMVD when administered at a daily dose of 0.1 mg/kg. The clinical pathology, gross necropsy, and histopathology findings were related to the expected pharmacological effects of a loop diuretic.

User Safety
The labeling for UpCard®-CA1 contains information about the safety to people who handle, administer, or are exposed to the drug.

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

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I. GENERAL INFORMATION

A. File Number

Application number 141-577

B. Sponsor

Vetoquinol USA, Inc.
4250 N. Sylvania Ave.
Fort Worth, TX 76137

Drug Labeler Code: 017030

C. Proprietary Name

UpCard®-CA1

D. Drug Product Established Name

torsemide oral solution

E. Pharmacological Category

Loop diuretic

F. Dosage Form

Oral Solution

G. Amount of Active Ingredient

2 mg/mL

H. How Supplied

Solution is packaged in bottles containing 32 or 96 mL

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

UpCard®-CA1 should be administered orally once daily at a dose of 0.05 to 0.2 mg/lb (0.11 to 0.44 mg/kg) of bodyweight.

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indication

For use with concurrent therapy with pimobendan, spironolactone, and an angiotensin converting enzyme (ACE) inhibitor for the management of pulmonary edema in dogs with congestive heart failure caused by myxomatous mitral valve disease (MMVD).

II. EFFECTIVENESS

Conditional Dose: The conditional dose for the indication "for use with concurrent therapy with pimobendan, spironolactone, and an angiotensin converting enzyme (ACE) inhibitor for the management of pulmonary edema in dogs with congestive heart failure caused by myxomatous mitral valve disease (MMVD)" is 0.05 to 0.2 mg/lb (0.11 to 0.44 mg/kg) of bodyweight once daily. The safety data and the data to demonstrate reasonable expectation of effectiveness provide support for this conditional dose.

A. Dosage Characterization

The dose of UpCard®-CA1 is based on the results of two laboratory studies conducted in healthy dogs that measured urine excretion after administration of torsemide. In study 182VD7F1, dogs were administered torsemide at a single oral dose of 0.05 to 10 mg/kg. Both the 0.05 and 0.1 mg/kg doses resulted in increases in urine output by approximately 50%. The greatest mean percentage increase in urine output was observed at 5 mg/kg. Study 182VD7F2 compared doses of torsemide between 0.15 and 4.5 mg/kg/day, administered orally for 5 days. Doses of 0.15 mg/kg and 0.4 mg/kg resulted in a mean percentage increase in urine output ranging from 33-50% and 181-328%, respectively. At a dose of 0.75 mg/kg, urine output was not statistically significantly different from that observed at doses of 1.5 and 4.5 mg/kg.

The dose of UpCard®-CA1 was also based on the results of two field studies conducted in client-owned dogs diagnosed with cardiac disease. In field study 182VC1F1, 176 dogs with congestive heart failure received torsemide tablets orally at a dose of 0.2-0.8 mg/kg/day with dose adjustments of 0.2 mg/kg/day or furosemide tablets orally at a dose of 1-5 mg/kg administered twice daily. Of these dogs, 132 were included in the effectiveness analysis. The results of this pilot field study suggested that the effectiveness of torsemide was non-inferior to treatment with furosemide (reported response rate at Day 84 was 68.7% and 63.1% for torsemide and furosemide, respectively; odds ratio of 1.277 and corresponding 97.5% confidence interval of 0.564, 2.889). However, an increased frequency of renal adverse events was seen among torsemide-treated dogs compared to the furosemide-treated dogs.

Based on these findings, a second field study (182VC1F2, see below under "Reasonable Expectation of Effectiveness") was conducted with a revised torsemide dose of 0.2-0.6 mg/kg/day and dose adjustments of 0.1 mg/kg/day, with a low dose of 0.1 mg/kg/day allowed starting at Day 7. The effectiveness of torsemide during this field study was again found to be non-inferior to treatment with furosemide with an acceptable adverse event profile.

B. Reasonable Expectation of Effectiveness

Reasonable expectation of effectiveness for UpCard®-CA1 for use with concurrent therapy with pimobendan, spironolactone, and an ACE inhibitor for the management of pulmonary edema in dogs with congestive heart failure caused by MMVD is based on the results of a multi-center European field effectiveness study (No. 182VC1F2) conducted with a tablet formulation of torsemide at a dose of 0.045 to 0.27 mg/lb (0.1 to 0.6 mg/kg), similar to the conditionally approved dose of 0.05 to 0.2 mg/lb (0.11 to 0.44 mg/kg). A pharmacokinetic (PK) bridging study (No. 1906VP2F1) demonstrated similar bioavailability between UpCard®-CA1 and the tablet formulation of torsemide used in study No. 182VC1F2.

1. Field Study

   Title: Confirmation of the Efficacy and Safety of Torsemide Tablets Compared to Furosemide in the Treatment of Congestive Heart Failure in Dogs through the Control of Oedema and Effusions. (Study No. 182VC1F2)

   Study Dates: April 2011 to January 2014

   Study Locations: Veterinary clinics located in France, Spain, and Germany from the following locations participated in the study.

Rennes, France	Ville Fontaine, France
Marseille, France	Ecole-Valentin, France
Strasbourg, France	Saint-Aubin-de-Blaye, France
Bonchamp-les-Laval, France	Beziers, France
Sanary-sur-Mer, France	Colombes, France
Ibos, France	Maisons-Alfort, France
Craponne, France	Soustons, France
Annecy, France	Pamplona, Spain
Nay, France	Logrono, Spain
Cavignac, France	Zaragoza, Spain
Corbeil-Essonnes, France	San Sebatian, Spain
Urrugne, France	Azugueca de Henares, Spain
La Rochelle, France	Mutilva Alta, Spain
Montfort-l'Amaury, France	Leon, Spain
Nogent-sur-Marne, France	Grafelfing, Germany
Annecy, France	Eisenach, Germany
Rambouillet, France	Hohenschonberg, Germany
Mont-de-Marsan, France	Obertshausen, Germany
Limoges, France	Eisenach, Germany
Argenteuil, France	Amerang, Germany
Haguenau, France	
Grenonle, France	

Study Design:

Objective: The objective of this study was to evaluate the effectiveness and safety of torsemide administered once daily for 3 months at a dose of 0.1 to 0.6 mg/kg/day, depending on the severity of disease, in comparison with another loop diuretic (furosemide), for the treatment of edema and effusions secondary to congestive heart failure.

Study Animals: A total of 251 client-owned dogs were enrolled in the study, with 148 males and 103 females (neutered/spayed or intact). Enrolled dogs ranged from 2.7 to 17.6 years of age and 6.6 to 162.8 lb (3.0 to 74.0 kg) bodyweight. Most were older, small-breed dogs, with a mean age of 11.7 years and median body weight of 25.6 lb. (11.6 kg). The most common breeds were mixed breed (21.5%), Poodles (14.4%), Yorkshire terriers (12.7%), and Cavalier King Charles Spaniels (10%).

Enrolled dogs were diagnosed with class II, III, or IV heart failure based on the modified New York Heart Association (NYHA) scoring system[1] and either presented with or had a history of at least one episode of pulmonary edema, pleural effusion, or ascites due to their heart failure. Dogs with acute pulmonary edema, pleural effusion, or ascites requiring emergency treatment with injectable drugs and dogs with congenital heart disease were excluded. Pregnant or lactating bitches; dogs with acute renal failure, anuria, or glomerulonephritis; and dogs with concurrent disease that would make it difficult to treat or assess the management of heart failure were also excluded from the study.

Experimental Design: This multi-site field study was conducted in accordance with Good Clinical Practice (GCP) guidelines and included two treatment groups, as summarized in Table II.1. The primary effectiveness variable was the response rate to treatment at Day 84. A dog was considered to have a successful response to treatment if the dog remained clinically stable compared to Day 0 AND pulmonary edema and/or pleural effusion and/or ascites had not worsened compared to the time of the dog's inclusion in the study. On Day 0, the dogs transitioned to either torsemide tablets or furosemide tablets. Dogs diagnosed with MMVD that were clinically stable and had received furosemide for at least 10 days prior to enrollment were included in the analysis for reasonable expectation of effectiveness.

[1] Class II: dogs with heart disease that causes clinical signs (fatigue, dyspnea, cough, etc.) during intense or extended physical activity.
Class III: dogs with heart disease that causes clinical signs during moderate physical activity.
Class IV: dogs with heart disease that causes clinical signs at rest.

Table II.1: Treatment Groups (Study No. 182VC1F2)

Treatment Group	Dose	Safety Population	Effectiveness Population
Torsemide tablets	0.1 to 0.6 mg/kg once daily	126	25
Furosemide tablets	1 to 5 mg/kg twice daily	125	36

Drug Administration: All dogs received treatment with torsemide or furosemide for three consecutive months. Dogs received either torsemide tablets at a starting dose of 0.2 to 0.6 mg/kg once a day, that could be adjusted as needed after Day 7, in increments of 0.1 mg/kg/day, between a dose of 0.1 and 0.6 mg/kg; or furosemide tablets at a starting dose of 1 to 5 mg/kg twice a day, that could be adjusted in increments of 1 mg/kg between a dose of 1 and 5 mg/kg twice a day. Concomitant treatment with standard of care therapy for congestive heart failure was allowed during the study if therapy was initiated prior to enrollment. Concomitant treatments included ACE inhibitors, pimobendan, digoxin, calcium channel blockers, and beta blockers.

Measurements and Observations: The dogs were examined by the clinical investigators at inclusion (Day 0, start of treatment), Day 7, Day 28, Day 56, and Day 84 (end of the follow-up period). At all visits, a full clinical examination was conducted, accompanied by thoracic radiographs and full biochemistry, hematology, and ionogram analysis. Dogs were staged according to the International Renal Interest Society (IRIS) system. Cardiac ultrasound was performed on Days 0 and 84.

Results: Of the 251 dogs that were enrolled in the study, 61 dogs with MMVD were considered appropriate for evaluation of the primary endpoint to support reasonable expectation of effectiveness because they were clinically stable and had received furosemide for at least 10 days prior to enrollment. After enrollment, 25 of these dogs were transitioned to torsemide tablets, and 36 dogs continued to be treated with furosemide.

The primary endpoint was response rate at Day 84; a dog was considered to have a successful response to treatment if pulmonary edema and/or pleural effusion or ascites had not worsened compared to Day 0. The success rates were 96.0% (24/25) for the torsemide group and 80.6% (29/36) for the furosemide group.

Adverse Reactions: A greater overall frequency of adverse events was recorded in the torsemide group (n = 184 events) compared with the furosemide treatment group (n = 104 events).

The most common adverse reactions associated with torsemide administration involved the urinary system, including polyuria and polydipsia, renal insufficiency, increased BUN and serum creatinine, and urinary incontinence. These findings were noted at greater frequency in torsemide-treated dogs than in the furosemide treatment group.

A relative increase in the risk of serious adverse events due to renal insufficiency (including increased BUN and serum creatinine and renal failure) was observed among torsemide-treated dogs compared with furosemide-treated dogs. Median BUN and serum creatinine levels were greater across all time points in torsemide-treated dogs and were still high in this group on day 84.

Electrolyte disturbances, including hypokalemia, hypochloremia, hypercalcemia, and hypomagnesemia, were also associated with torsemide therapy. Diarrhea, vomiting, inappetence, and lethargy were also noted in torsemide-treated dogs.

Clinical findings associated with the worsening of congestive heart failure noted in torsemide-treated dogs included cough, dyspnea, pulmonary edema, and cardiac arrest.

A total of 30 dogs died during the study, 12 in the torsemide group and 18 in the furosemide group. Euthanasia was the most common cause of death with similar frequency between the treatment groups, and was due to progression of renal failure, deterioration of condition, acute pulmonary edema, acute cardiac death, accidental death, death from another disease condition, or unknown cause.

Conclusions: The results of this field study demonstrate a reasonable expectation of effectiveness for UpCard®-CA1 for use with concurrent therapy with pimobendan, and an ACE inhibitor for the management of pulmonary edema in dogs with congestive heart failure caused by MMVD. Treatment with torsemide is associated with polyuria/polydipsia, renal insufficiency (including increased BUN and serum creatinine and renal failure), urinary incontinence, and electrolyte disturbances (including hypokalemia, hypochloremia, hypercalcemia, and hypomagnesemia).

2. Pharmacokinetic Bridging Study

Title: Determination of Plasma and Urinary Pharmacokinetic Parameters of Torasemide[2] in Dogs after Oral Administration of a 0.2% Solution at a Dose of 0.1 mg/kg and Evaluation of the Relative Bioavailability versus UpCard® Tablets. (Study No. 1906VP2F1)

Study Dates: November 9, 2017 to December 18, 2019

Study Location: Lure, France

Study Design:

Objective: The objective of this study was to determine the kinetic parameters of torsemide in plasma and urine of dogs following a single administration of UpCard®-CA1 (torsemide oral solution) at a dose of 0.1 mg/kg, and to evaluate

[2] Torasemide and torsemide are used interchangeably to describe the same active pharmaceutical ingredient.

the relative bioavailability of the oral solution versus torsemide tablets using a cross-over design.

Study Animals: The study included 10 clinically healthy Beagle dogs, 5 females and 5 males, between about 3.2 and 4.1 years old and weighing between 28.4 and 42.0 lb (12.9 and 19.1 kg).

Experimental Design: This randomized, masked laboratory PK study was conducted in accordance with Good Laboratory Practice (GLP) regulations. This 2-period, 2-sequence cross-over study had a washout of 14 days between each period and included 2 treatment groups, as shown in Table II.2.

Table II.2: Treatment Groups (Study No. 1906VP2F1)

Treatment Group	Period 1 Treatment and Dose	Period 2 Treatment and Dose
Group 1	UpCard®-CA1 0.1 mg/kg	Torsemide tablets 0.1 mg/kg
Group 2	Torsemide tablets 0.1 mg/kg	UpCard®-CA1 0.1 mg/kg

Drug Administration: Treatments were administered to fasted animals. Tablets were administered into the back of the mouth followed by a small amount of water. The most appropriate number of ¼ tablets were administered based on weight bands to achieve a dosage of 0.11 – 0.13 mg/kg. UpCard®-CA1 was administered by the oral route, at a dose of 0.1 mg torsemide/kg bodyweight corresponding to a volume of 0.05 mL/kg.

Measurements and Observations: Blood samples were obtained by venipuncture of the right or left jugular vein at the following time points: 0, 15, 30 min, and 1, 1.5, 2, 4, 6, 8, 10, 24, 32, 48, 56, and 72 hours after the oral administrations. The entire volume of excreted urine was collected from a metabolism cage at 0, 2, 4, 6, 8, 10, 24, 32, 48, 56, and 72 hours after dose administration.

Torsemide analysis in plasma samples was performed using a validated liquid chromatography (LC) with tandem mass spectrometry (MS) detection assay. The limit of quantification (LOQ) of the method was 0.01 µg/mL. Torsemide analysis in urine samples was performed using a separate LC/MS method with an LOQ of 0.03 µg/mL.

Statistical Methods: The individual plasma data sets were analyzed using Phoenix® WinNonlin software (version 6.3). The relative bioavailability of torsemide was calculated with plasma (F_R) and urine (F_{Ru}) data, respectively, as follows:

F_R (%) = (UpCard®-CA1 AUC_{inf} / Tablet AUC_{inf}) * (Tablet Dose / UpCard®-CA1 Dose) * 100

F_{Ru} (%) = (UpCard®-CA1 X_u^∞ / Tablet X_u^∞) * (Tablet Dose / UpCard®-CA1 Dose) * 100

Area under the curve from the time of dosing extrapolated to infinity (AUC_{inf}) of torsemide in plasma, total excreted amount of torsemide in urine (X_u^∞), and actual administered doses were used.

Results: Plasma and urine PK parameters calculated using non-compartmental analysis after a single 0.1 mg/kg orally administered dose of torsemide tablets or UpCard®-CA1 are presented in Table II.3.

Table II.3: Plasma and Urine Torsemide Pharmacokinetic Parameters in Dogs after a Single 0.1 mg/kg Oral Dose of Torsemide Tablets or UpCard®-CA1

Parameter	Torsemide Tablets Mean (Confidence Limits)	UpCard®-CA1 Mean (Confidence Limits)
T_{max}[a] (h)	1.0 (0.5 to 1.5)	0.75 (0.5 to 1.0)
C_{max} (µg/mL)	1.39 (0.863 - 2.22)	1.20 (0.840 - 1.71)
$t_{½}$ (h)	7.43 (4.25 - 13.0)	7.68 (4.79 - 12.3)
AUC_{last} (µg*h/mL)	7.94 (3.93 - 16.0)	7.17 (4.35 - 11.8)
F_R (%)	-	100 (62.8 - 160)
Urine Volume (mL)	1140 (623 - 2080)	1040 (562 - 1940)
X_U^∞ (µg)	1200 (805 - 1790)	1010 (661 - 1540)
%Dose (%)	68.8 (54.1 - 87.5)	64.0 (48.8 - 83.8)
F_{Ru} (%)	-	93.1 (70.6 - 123)

[a] Values provided for T_{max} are median (and range); values for the other parameters are geometric mean (95% confidence limits).
T_{max} = time to maximum plasma concentration
C_{max} = maximum plasma concentration
$t_{1/2}$ = elimination half-life
AUC_{last} = area under the plasma concentration curve from the time of dosing to the last quantifiable concentration
F_R: relative bioavailability in plasma
Urine Volume: total excreted urine volume
X_u^∞: total excreted amount of torsemide in urine
%Dose: percentage of the actual administered dose of torsemide eliminated in urine as parent drug
F_{Ru}: relative bioavailability in urine

Conclusions: The relative bioavailability of torsemide in plasma and urine from UpCard®-CA1 compared to the tablet formulation used in the field study to demonstrate reasonable expectation of effectiveness was high (100% and 93.1%, respectively). Therefore, similar diuretic activity and safety profiles are expected following administration of each formulation. Additionally, administration of torsemide as an oral solution formulation rather than with tablets will allow for more precise adjustments towards achieving the minimum effective dose, and therefore may minimize renal safety issues.

III. TARGET ANIMAL SAFETY

The safety of UpCard®-CA1 was supported by two laboratory studies in the target species (dogs): a six-month margin of safety study in 32 dogs using the proposed

commercial oral solution formulation and a 13-week margin of safety using torsemide tablets. Field safety was supported by two European clinical field studies (summarized above) that enrolled a total of 213 dogs administered torsemide tablets. Field safety was further supported by drug experience reporting from the European market.

A. Margin of Safety Study

Title: Torsemide: Six-month Oral Repeat-Dose Target Animal Safety Study in Dogs. (Study No. 036327)

Study Dates: May 8, 2019 to January 19, 2021

Study Location: Concord, OH

Study Design:

Objective: The objectives of this study were to evaluate the toxicity and the exposure of animals following repeated oral administration of UpCard®-CA1 to healthy male and female Beagle dogs for six months.

Study Animals: The study included 32 healthy Beagle dogs (16 male and 16 female), non-pregnant, non-lactating, approximately 6 months of age and weighing between 4.95 and 7.50 kg at the beginning of the treatment period.

Experimental Design: The study was a masked, randomized, controlled margin of safety laboratory study. Dogs were randomly allocated to four treatment groups (0X, 0.25X, 1.0X, 1.5X) of eight dogs each. UpCard®-CA1 (0.2% torsemide oral solution) was administered once daily for 6 months (184 doses) at 0.25X, 1.0X, and 1.5X the maximum daily recommended therapeutic dose (0.11, 0.44, 0.66 mg/kg/day, respectively). The control dogs (0X, 0 mg/kg/day) were administered 0.9% sodium chloride at a comparable volume as to that administered to the 1.5X group. The study was conducted in accordance with GLP regulations.

Table III.1: Treatment Groups in Study No. 036327

Treatment Group	Number and Sex of Animals	Test Article	Dose (mg/kg/day)	Dose Volume (mL/kg)
1 (0X)	4 male and 4 female	Control	0	0.33
2 (0.25X)	4 male and 4 female	UpCard®-CA1	0.11	0.055
3 (1.0X)	4 male and 4 female	UpCard®-CA1	0.44	0.22
4 (1.5X)	4 male and 4 female	UpCard®-CA1	0.66	0.33

Drug Administration: The test article was the commercial formulation of UpCard®-CA1 (0.2% torsemide oral solution). Dogs were administered the appropriate dose of test article, based on treatment group, according to their latest body weight. The test articles were administered orally by syringe once a day, concurrent with feeding

(which was shown in a separate study to significantly increase torsemide exposure by 24%), for 26 weeks.

Measurements and Observations: Clinical observations were performed twice daily. Other daily assessments included the post-dose emesis check and food consumption. Weekly assessments included body weight measurements, detailed clinical observations, and water consumption (for a 24-hour period). Veterinary examinations, electrocardiography (ECG), blood pressure (BP), and body temperature measurements were conducted prior to the start of dosing, during Weeks 1, 4, and 13, and the final week of the dosing period. Ophthalmologic examinations were conducted pre-dose, during Week 13, and the final week of the dosing period. Hematology, coagulation, serum chemistry, and urinalysis parameters were assessed pre-dose, during Weeks 4 and 13, and the final week of the dosing period.

In order to determine exposure levels, plasma samples for bioanalytical assessment were collected on Day 0, during Weeks 4 and 13, and on the last day of dosing. The samples were analyzed for torsemide concentration using a validated LC/MS method.

Statistical Methods: The unit of observation and statistical analysis was the individual dog. Statistical comparisons were performed two-sided, at the 0.1 level of significance except for the three-way interaction which was at 0.05 significance level. Continuous variables measured at multiple times during the study were analyzed by a repeated measures analysis of covariance, with treatment, time, sex, treatment by sex, treatment-by-time, sex-by-time, and treatment-by-sex-by-time as fixed effects, and room as random effect (the MIXED procedure in SAS, RMANCOVA). Torsemide plasma concentration values were analyzed by repeated measures analysis of variance (RMANOVA) including the same fixed and random effects. The last available pre-treatment value was used as a baseline covariate. The covariance structure was selected from the following: compound symmetry (CS), compound symmetry heterogenous variances (CSH), and unstructured (UN). For body weights, on which measurement intervals were equally spaced, the first-order autoregressive [AR(1)] and first-order autoregressive heterogenous variances [ARH(1)] were also considered. The RANDOM statement was included with the AR(1) and ARH(1) models. The Kenward-Roger (KR) approximation for denominator degrees of freedom was used. The minimum Akaike Information Criterion was used to select the covariance structure.

Results: Weekly average food consumption decreased starting during Week 1 and remained lower for the duration of the study for both 1.5X male and female dogs, occasionally reaching statistical significance in comparison to the control group. In the 0.25X and 1X groups, food consumption was lower in general in comparison with the control group, but the differences were not statistically significant except for a lower food consumption at Week 3 for the 1X female dogs.

Body weight decreased in the groups administered torsemide. In the 0.25X group, mean weekly body weights decreased up to 4.6%, but the differences were not statistically significant in comparison to the control group. In the 1X and 1.5X groups, mean weekly body weights decreased up to 9.4% and 11.8%, respectively; the

differences were statistically significant in comparison to the control group at sporadic timepoints throughout the study.

There was no apparent effect on daily water consumption in the 0.25X or 1X groups compared to the control group. The 1.5X group had increased daily mean water consumption starting on Days 28-29 in male dogs and on Days 56-57 in female dogs. At these time points, the dogs in the 1.5X group consumed approximately twice the amount of water as the control dogs.

Dogs in the 1X and 1.5X groups had changes in clinical pathology parameters during Weeks 4 and 13, and the final week of the dosing period. In the 1X and 1.5X groups, erythroid changes consisted of increased red cell mass parameters (red blood cell count, hemoglobin, and hematocrit) and were consistent with hemoconcentration as a result of dehydration secondary to diuresis. Serum chemistry changes in these groups consisted of increased albumin, BUN, and creatinine; and decreased chloride and potassium. Increased BUN and creatinine were consistent with dehydration secondary to diuresis or a direct test article-related effect on the kidneys. Decreased chloride and potassium were attributed to the diuretic effect of the test article. Torsemide administration in the 0.25X group had no effect on clinical pathology parameters.

Dogs in the 1X and 1.5X groups had changes in urinalysis parameters. The changes consisted of decreased urine specific gravity and increased urine volume.

Torsemide administration had no observed adverse effects on ophthalmologic examination, electrocardiography, blood pressure, and body temperature.

Torsemide plasma concentrations were statistically higher at each time point for the 1X and 1.5X groups when compared to the 0.25X group and were statistically higher at each time point for the 1.5X group when compared to the 1X group. Plasma concentrations were similar for males and females.

Systemic exposure (AUC) increased in a dose proportional manner between the 0.1 and 0.6 mg/kg groups. At 1X, accumulation was minimal (approximately 30%) with steady state being reached by Week 4, the first sample timepoint after Day 0.

There was no mortality, moribundity, or serious adverse reactions observed during the study. Torsemide-related clinical observations included reduced fecal amounts in 1X and 1.5X group dogs and, in individual animals, general body conditions or activity level findings including thin body appearance in 1X and 1.5X group dogs, reduced activity or lethargy in one 1.5X male dog, and dehydration in 1X and 1.5X male and 1.5X female dogs.

During the first week of the dosing period, individual male and female dogs in the 1X and 1.5X groups were noted with very low food consumption, dehydration, and/or body weight loss. More palatable noncertified Purina dog chow was mixed in the diet of all dogs for a few days to stimulate appetite and Lactated Ringer’s solution was administered to dogs exhibiting dehydration (4 animals).

Conclusion: The study demonstrated that UpCard®-CA1 Oral Solution (torsemide oral solution) has an adequate margin of safety for management of pulmonary edema related to congestive heart failure in dogs with MMVD when administered at doses up to 0.66 mg/kg or 1.5X the maximum labeled dose for 6 months. The clinical observations noted in the study were related to the expected pharmacological effect of administering a loop diuretic in healthy dogs.

B. Supportive Target Animal Safety Study

Title: A 13 Week Study of Torsemide Tablets by Oral Administration in Dogs. (Study No. 521868)

Study Dates: May 30, 2012 to October 02, 2013

Study Location: Edinburgh, United-Kingdom

Study Design:

Objective: The objective of this safety study was to evaluate the toxicity and the exposure of animals following oral administration of torsemide tablets to healthy male and female Beagle dogs for three months.

Study Animals: The study included 32 healthy Beagle dogs (16 male and 16 female), non-pregnant, non-lactating, approximately 5 months of age and weighing between 4.0 and 8.0 kg at the beginning of the treatment period.

Experimental Design: The study was a masked, randomized, controlled margin of safety laboratory study. Dogs were randomly allocated to four treatment groups (0X, 0.23X, 0.68X, and 1.36X) of eight dogs each. Torsemide tablets were administered once daily for 13 weeks at 0.23X, 0.68X, and 1.36X of the maximum daily recommended therapeutic dose (0.1, 0.3, 0.6 mg/kg/day, respectively). The control dogs (0X, 0 mg/kg/day) were administered placebo tablets at a comparable quantity as to that administered to the 1.36X group. The study was conducted in accordance with GLP regulations.

Table III.2: Treatment Groups in Study No. 521868

Treatment Group	Number and Sex of Animals	Test Article	Dose (mg/kg/day)
1 (0X)	4 male and 4 female	Placebo tablets	Equivalent to 0.6 mg/kg/day dose
2 (0.23X)	4 male and 4 female	Torsemide tablets	0.1
3 (0.68X)	4 male and 4 female	Torsemide tablets	0.3
4 (1.36X)	4 male and 4 female	Torsemide tablets	0.6

Drug Administration: The test article was supplied as white to off-white oblong tablets containing 0.75 or 3 mg of torsemide, or placebo, with one breaking line on both sides. Dogs were administered the appropriate dose of test article, based on

treatment group, according to their latest body weight. The test articles were administered orally once a day, with food (which was shown in a separate study using the tablets to significantly increase torsemide exposure by 39%), for 13 weeks.

Measurements and Observations: Viability, clinical signs, body weights, body weight changes, food and water consumption, ophthalmology, electrocardiography and blood pressure, clinical pathology parameters (hematology, coagulation, clinical chemistry, aldosterone analysis, urinalysis, fecal occult blood, and whole blood clotting times), toxicokinetic parameters, gross necropsy findings, organ weights, and histopathological examinations were evaluated in this study.

Statistical Methods: Statistical tests were conducted at the 0.10 level of significance. Statistical analysis was performed using SAS (v8.2). The unit of observation and statistical analysis was the individual dog. Body weight and water consumption were analyzed using a mixed model analysis of covariance for repeated measures design. Pre-treatment values were included in the model as a covariate. Fixed effects terms for baseline value (covariate), sex, time and treatment group and fixed effect interactions for sex by treatment group, sex by time, treatment group by time and sex by treatment group by time were included in the model. Animal number was included as a random effect, where appropriate. For food consumption, no covariate was included in the model. Hematology, coagulation, clinical chemistry, and selected urinalysis data were analyzed in an identical way to body weights with baseline defined as prior to dosing initiation. The variance-covariance structure was assessed using the following sequence of models: compound symmetry (CS), heterogeneous compound symmetry (CSH), autoregressive of order 1 (AR[1]), autoregressive heterogeneous of order 1 (ARH[1]). The final model used was the one with the lowest Akaike Information Criterion.

Organ weight data was analyzed for each organ separately using a mixed model analysis of covariance. For paired organs, paired organ weights were analyzed. PK parameters for toxicokinetic evaluation were estimated using WinNonlin PK software version 5.2.1 (Pharsight) using a non-compartmental approach.

Results: Clinical observations consisted of slight and reversible reaction in the inner pinna (reddened and/or small red spots) of the dogs that received 0.6 mg/kg/day that appeared to be related to the administration of the test article. This was also observed, although to a lesser frequency and extent, in animals that received 0.3 mg/kg/day.

In the 0.6 mg/kg/day dose group, an increase in water consumption was observed from Week 4 onwards. No changes in food consumption or body weight were observed in any groups.

Clinical pathology findings of dogs administered torsemide at 0.1, 0.3, and 0.6 mg/kg/day were generally mild and did not reach clinical significance.

Increases in red cell mass parameters (hemoglobin, red blood cell count, and hematocrit), in comparison to baseline data, were observed during Week 8 and 13 in the 0.1 mg/kg/day group, and increased albumin concentrations in males at ≥ 0.3 mg/kg/day and in females at ≥ 0.1 mg/kg/day were observed throughout the

treatment period. These changes were most likely related to hemoconcentration/dehydration, secondary to the diuretic effect of torsemide tablets.

Increases in serum urea concentrations in males in the 0.6 mg/kg/day group and females receiving ≥ 0.1 mg/kg/day, and increased serum creatinine concentrations in males receiving ≥ 0.3 mg/kg/day and females receiving ≥ 0.1 mg/kg/day were observed by the conclusion of the treatment period. Minimal decreases in potassium concentrations were observed in males and females receiving ≥ 0.3 mg/kg/day at the end of the treatment period, with transient decreases in males receiving 0.1 mg/kg/day during Week 4. Minimal decreases in chloride concentrations were observed in males receiving 0.6 mg/kg/day and in females receiving ≥ 0.3 mg/kg/day throughout the treatment period. Minimally decreased inorganic phosphate concentrations were present by the end of the treatment period in males and females receiving ≥ 0.3 mg/kg/day. Minimal decreases in total calcium and magnesium concentrations were seen in males and females receiving 0.6 mg/kg/day, during Week 8 and Week 13. These changes are likely related to the pharmacological activity of torsemide.

The kidneys of all dogs that received 0.6 mg/kg/day were enlarged, with microscopic correlates of basophilic tubular epithelial cells in the renal cortex and outer medulla, tubular dilation of the proximal and distal tubules, mononuclear cell infiltration, and tubular mineralization observed in several animals. These histopathological changes were considered to be related to the pharmacological action of torsemide.

Systemic exposure (AUC) increased in a dose proportional manner between the 0.1 and 0.6 mg/kg groups. Accumulation was minimal (approximately 20%) with steady state being reached by Week 4, the first sample timepoint after Day 0.

Conclusions: The study demonstrated that torsemide has an adequate margin of safety for management of pulmonary edema related to congestive heart failure in dogs with MMVD when administered at 0.1 mg/kg/day, and supports the safety of the label dose of 0.11 to 0.44 mg/kg/day. The clinical observations noted in the study were related to the expected pharmacological effect of administering a loop diuretic in healthy dogs.

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 UpCard®-CA1:

Not for use in humans. Keep this and all medications out of the reach of children. **Wash hands after use and/or spillage.**

In case of accidental human ingestion, seek medical advice immediately and show package insert or the label to the physician. Symptoms of exposure to torsemide

may include dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, nausea, or vomiting. Additionally, exposure may induce hypovolemia and result in hyperglycemia, hypokalemia, shunt thrombosis, syncope, and ventricular tachycardia.

VI. AGENCY CONCLUSIONS

The data submitted in support of this application satisfy the requirements of section 571(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The data demonstrate that UpCard®-CA1, when used according to the label, is safe and has a reasonable expectation of effectiveness for the conditions of use in the General Information Section above.

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.

UpCard®-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. Pulmonary edema in dogs with congestive heart failure caused by MMVD is considered a serious and life-threatening disease because, when left untreated, this disease is fatal to dogs. A demonstration of effectiveness requires a complex study design because the nature of the disease makes it time consuming and difficult to enroll sufficient numbers of eligible animals to provide substantial evidence of effectiveness. Additionally, diagnosis of the disease requires the use of advanced and complicated tests.

B. Marketing Status

UpCard®-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 and manage congestive heart failure caused by MMVD, and to monitor the safe use of the product, including the management of any adverse reactions associated with the drug.

C. Exclusive Marketing Rights

UpCard®-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.