Date of Approval: May 6, 2026

FREEDOM OF INFORMATION (FOI) SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION (NADA)

NADA 141-627

Tessie®

(tasipimidine oral solution)

Dogs

For the treatment of noise aversion and separation anxiety in dogs.

Sponsored by:

Orion Corp.

Executive Summary

Tessie® (tasipimidine oral solution) is approved for the treatment of noise aversion and separation anxiety in dogs. Tasipimidine, the active ingredient in Tessie®, is an alpha-2 adrenoceptor agonist. Tessie® is available in a clear 20 mL glass bottle (containing 15 mL of dosing solution) with child resistant closure and fitted syringe adapter. The bottle is packaged in a carton with a 3 mL oral syringe. Tessie® can be given up to 3 times within 24 hours, with at least 3 hours between doses.

Safety and Effectiveness

The effectiveness of Tessie® for noise aversion was demonstrated in one well-controlled clinical field study in 160 client-owned dogs. The field study demonstrated that Tessie® was safe and effective for the treatment of noise aversion when administered as needed at the dose of 30 mcg/kg, up to 3 times, during the noise event with at least 3 hours pause between the doses. The most common adverse reactions reported in the Tessie® treated group were vomiting and lethargy.

The effectiveness of Tessie® for the treatment of separation anxiety was demonstrated in one well-controlled 8-week clinical field study in 224 client owned dogs. The field study demonstrated that Tessie® was safe and effective for the treatment of separation anxiety when administered 1 hour before owner departure at the dose of 30 mcg/kg, or the dose of 20 mcg/kg if indicated due to reduced alertness. The product was used as needed up to 2 times a day with at least 3 hours pause between the doses. The most common adverse reactions reported in the Tessie® treated group were vomiting, diarrhea, and lethargy.

The sponsor conducted two laboratory margin of safety studies in healthy Beagle dogs, one 28-day study and one 6-month study. In the first study, dogs were administered tasipimidine at 30, 150, and 510 mcg/kg once daily by oral gavage for 28 days. Clinical signs were similar in each group (lethargy, lateral recumbency, vomiting, and salivation), with a dose dependent increase in number, length, and severity of the signs. There was a dose-dependent decrease in heart rate and blood pressure at all doses. In the second study, dogs were administered Tessie® at 30, 90, or 150 mcg/kg twice daily (orally/via oral gavage) for 6 months. Dogs in all treated groups showed dose dependent sedation related effects, including ataxia/abnormal gait, lateral recumbency, partly closed eyes, and decreased activity. In all dogs, signs of sedation resolved prior to dosing on the next day.

Conclusions

Based on the data submitted by the sponsor, the Food and Drug Administration (FDA) determined that the drug is safe and effective when used according to the labeling.

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I. GENERAL INFORMATION

A. File Number

NADA 141-627

B. Sponsor

Orion Corp.
Orionintie 1
02200 Espoo
Finland

Drug Labeler Code: 052483

U.S. Agent Name and Address:

Sharon G. Chase, D.V.M., M.P.H.
Clinaxel Inc.
170 State Route 17C
Waverly, NY 14892

C. Proprietary Name

Tessie®

D. Drug Product Established Name

tasipimidine oral solution

E. Pharmacological Category

Alpha-2 adrenoceptor agonist

F. Dosage Form

Solution

G. Amount of Active Ingredient

Each mL of Tessie® contains 0.3 mg tasipimidine (equivalent to 0.427 mg tasipimidine sulfate)

H. How Supplied

Tessie® is packed in a clear glass bottle (containing 15 mL of dosing solution) with a child resistant closure and adapter. The bottle is further packed into a carton with a package insert and an oral syringe.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

Tessie® is administered orally at the dose of 0.1 mL/kg (30 mcg/kg). However, it is recommended that a test dose is administered to confirm that this is the correct dose for the dog.

Avoid giving the product together with food as absorption may be delayed. Keep at least 1 hour between feeding and dosing. A small treat can be given to ensure that the dog swallows the solution. Water can be freely available.

Test dose:
When giving the very first dose, the dog should be observed for 2 hours to make sure that the dose is appropriate for this dog. If the dog appears drowsy, its movements are uncoordinated or it responds to owner's call abnormally slowly after receiving treatment, the dose could be too high. In such case the dog should not be left alone. Future doses should be reduced to 2/3 of the volume of the previous dose, corresponding to 20 mcg/kg bodyweight. Dose reduction should be implemented following veterinary advice only.

Do not exceed the recommended dose. Dosing should be performed by an adult.

Treatment of noise aversion:
The first dose should be given 1 hour before expected start of a triggering noise stimulus (e.g. sound of fireworks), as soon as the dog shows the first signs of anxiety related to the noise, or when the owner detects a typical stimulus that causes anxiety in the respective dog. Depending on the level of arousal, the signs of noise aversion may not be completely eliminated.

Observe the dog. If the noise event lasts longer than 3 to 4 hours and the dog's signs of noise aversion reappear, another dose may need to be administered. To avoid overdosing, there should always be a pause of at least 3 hours between dosages. The product can be dosed up to 3 times within 24 hours.

Treatment of separation anxiety:
Give the dose 1 hour before leaving the dog alone. For further departures during the same day a new dose can be administered when at least 3 hours have passed from the previous dose. For the treatment of separation anxiety, the product can be administered up to 3 times within every 24 hours. Typical signs for separation anxiety are expressed only in absence of the owner or when owner prepares to leave the dog alone.

Do not administer Tessie® to dogs that are drowsy from previous dose(s). Do not leave your dog alone if it is drowsy after dosing of Tessie®.

K. Route of Administration

Oral

L. Species

Dogs

M. Indication

For the treatment of noise aversion and separation anxiety in dogs.

II. EFFECTIVENESS

The effectiveness of Tessie® for noise aversion was demonstrated in one well-controlled clinical field study in 160 client-owned dogs. The field study demonstrated that Tessie® was safe and effective for the treatment of noise aversion when administered as needed at the dose of 30 mcg/kg up to 3 times during the noise event with at least 3 hours pause between the doses. The effectiveness was measured both with a global score over the entire duration of the noise event as well as with repeated ratings of the behavioral signs indicative of noise aversion. The most common adverse reactions reported in the Tessie® treated group were vomiting and lethargy.

The effectiveness of Tessie® for the treatment of separation anxiety was demonstrated in one well-controlled 8-week clinical field study in 224 client-owned dogs. The field study demonstrated that Tessie® was safe and effective for the treatment of separation anxiety when administered 1 hour before owner departure at the dose of 30 mcg/kg, or the dose of 20 mcg/kg if indicated due to reduced alertness. The product was used as needed up to 2 times per day with at least 3 hours pause between the doses. The effectiveness was measured both with a global score of signs seen during the owner absence, as well as with ratings of the behavioral signs indicative of separation anxiety. The most common adverse reactions reported in the Tessie® treated group were vomiting, diarrhea, and lethargy.

A. Dosage Characterization

Based on the results of nonclinical studies, the doses of 10, 30, and 60 mcg/kg were selected to evaluate the effectiveness and safety of tasipimidine in client-owned dogs. In a field study in client-owned dogs that were difficult to handle in veterinary clinics due to fear or anxiety, three doses of tasipimidine oral solution (10, 30, and 60 mcg/kg) were evaluated against vehicle control. The 60 mcg/kg dose did not result in markedly increased effectiveness and the incidence of adverse events, especially those associated with lethargy or signs of sedation, was higher with the 60 mcg/kg dose than with the two lower doses. Therefore, the 60 mcg/kg dose was not included in subsequent clinical field studies.

Noise Aversion:

Title: Pilot Field Study in Dogs Suffering From Noise Aversion. (Study No. V3110003)

In this field study, the effectiveness and safety of two doses of tasipimidine oral solution (10 and 30 mcg/kg) were evaluated compared to a vehicle control for alleviation of canine acute anxiety and fear associated with noise due to fireworks in 43 client-owned dogs. This study was designed as a randomized, double-blind,

vehicle-controlled, dose-finding field study with three parallel groups. The study was conducted at one site in Finland. Forty-three dogs with history of noise aversion were randomized to study treatment: 29 dogs received tasipimidine (15 and 14 dogs received 10 and 30 mcg/kg, respectively) and 14 dogs received vehicle as needed up to 3 times.

Repeated doses were not allowed if the dog showed signs of decreased functional alertness. If the dog had shown decreased functional alertness in the previous assessment, the owner was instructed to contact the investigator for advice on possible dose reduction. Functional alertness was assessed using a combination of the dog's ability to stand up and walk and its overall responsiveness to the owner's call.

The dog owners used a predefined scale to assess the treatment effect on their dog's signs of acute anxiety. 92.8% of the owners in the 30 mcg/kg group scored the treatment effect on the signs of noise anxiety in their dog as either excellent or good, compared to 53.3% in 10 mcg/kg group and 35.7% in the control group.

A total of 10 adverse reactions (ARs) were reported in 9 treated dogs after start of the study treatment. Seven (16.3%) of the ARs were assessed as treatment related. No ARs were reported for dogs administered control. Decreased alertness was reported in 7% (1/15) of dogs treated with 10 mcg/kg and 21% (3/14) of dogs treated with 30 mcg/kg. In one of the dogs at each dose level, the last dose (second or third) was reduced due to sedation. Most of the dogs (25/29) were able to stand up and walk normally at 1 and 2 hours after each dose. There was only 1 dog in the 30 mcg/kg group that was unable to stand up and walk at 1 hour after the second dose. Vomiting was recorded in three dogs, two of which received tasipimidine at 10 mcg/kg and one that had received tasipimidine at 30 mcg/kg. Painful defecation was recorded in one dog that had received tasipimidine at 10 mcg/kg.

The treatment difference was statistically significant in favor of the 30 mcg/kg dose, whereas the difference between 10 mcg/kg and control was not significant. Based on the results of this study, the dose of 30 mcg/kg was selected for the pivotal effectiveness field study for the treatment of noise aversion.

Separation Anxiety:

Title: Pilot Field Study in Dogs Suffering From Separation Anxiety. (Study No. V3110004)

The effectiveness and safety of two doses of tasipimidine oral solution (10 and 30 mcg/kg) were evaluated compared to vehicle control for the treatment of separation anxiety in 12 client-owned dogs. This study was designed as a randomized, double-blind, vehicle-controlled, three-period crossover dose-finding field study. The study was conducted at one site in Finland. Dogs enrolled in the study received either tasipimidine (10 or 30 mcg/kg) or vehicle control, once a day 1 hour prior to owner departure on four consecutive days. A total of 12 dogs were randomized and went through each of the three treatments, with a 3-day washout between treatment periods. If the dog had shown decreased functional alertness in the functional

alertness assessment conducted on the first day of each treatment period, the dog was not given further doses during the given study period.

Treatment effect on dogs' signs of separation anxiety was assessed by owners using a predefined scale. To make the effectiveness assessments, the owners were able to observe their dog during separation in "real time" via video and they could also later review video recordings of their dog's behavior during separation. When compared to the days on the control, there was a statistically significant difference in effectiveness in the 30 mcg/kg treatment group. The difference in clinical signs of separation anxiety during the days on the 10 mcg/kg dose and the days on control group was not statistically significant. Based on the results of this study, the 30 mcg/kg dose was selected.

A total of 33 adverse reactions (ARs) were reported in nine dogs (out of 12 treated dogs) after start of the study treatment. Thirty-two (97%) of the ARs were assessed as treatment related. Lethargy was the most common adverse event reported; it was observed in six dogs during the 30 mcg/kg treatment period. There were no serious adverse reactions (SARs). Decreased functional alertness was reported for one dog in the 30 mcg/kg treatment period and that dog was not dosed on the following days. Two other dogs had treatment interruption due to ARs in a given treatment period.

Based on the results of this study, the dose of 30 mcg/kg was selected for the substantial evidence of effectiveness field study for the treatment of separation anxiety. It was also noted that for some dogs a dose reduction would be warranted.

B. Substantial Evidence

Noise Aversion:

1. Multi-site Field Effectiveness Study

   Title: Tasipimidine Oral Solution for Alleviation of Canine Acute Anxiety and Fear Associated With Noise. (Study No. V3110005)

   Study Dates: November 2016 to January 2017

   Study Locations:

   Helsinki, Finland
   Raisio, Finland
   Kaarina, Finland
   Turku, Finland
   Kangasala, Finland
   Freising, Germany
   Frontenhausen, Germany
   Elmshorn, Germany
   Traunreut, Germany
   Steingaden, Germany
   Münchsteinach, Germany
   Ebenhausen, Germany
   München, Germany
   Nürnberg, Germany
   Odder, Denmark
   Naestved, Denmark
   Glamsbjerg, Denmark
   Amares, Portugal
   Pardilho, Portugal
   Vila Verde, Portugal

Study Design:

Objective: The primary objective of this study was to confirm clinical safety and effectiveness of tasipimidine oral solution for the treatment of canine noise aversion, using fireworks as the eliciting stimulus.

Study Animals: A total of 160 client-owned, male and female, pure and mixed breed dogs were randomized and received study treatment: 80 dogs received tasipimidine at 30 mcg/kg and 80 dogs received vehicle control. The age of the dogs ranged between 2 to 14 years and body weight ranged between 3 to 60 kg. All dogs were healthy or were recorded to have mild systemic disease that was stable, and had previously shown signs of noise aversion associated with fireworks noise exposure.

Experimental Design: The study was a randomized, double-blind, vehicle-controlled study with two parallel groups. Dogs were randomized into two treatment groups in a 1:1 ratio of tasipimidine (30 mcg/kg) or control. The study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

Drug Administration: Study treatment was administered to the dog at home by the dog owner. The first dose was administered when the first (even distant) fireworks could be heard or the dog showed signs of anxiety or fear. The dose could be repeated if the dog showed signs of becoming anxious and fearful again. The maximum number of doses in the study was three and the minimum interval between doses was 3 hours. Re-dosing was not allowed in dogs showing decreased functional alertness.

Measurements and Observations: Dogs with previous history of noise aversion were eligible for study participation. The test day was New Year's Eve. A veterinarian examined the dog and interviewed the dog owner within 4 weeks before New Year's Eve. The owner performed the baseline assessments in the evening 2 to 5 days before New Year's Eve. Treatment was started as soon as distant fireworks were heard, or when the dog showed first signs of becoming anxious or fearful. The owner performed the safety assessments throughout the study and performed the effectiveness assessments concerning dog's signs and extent of anxiety and fear before treatment, at 1 hour after dosing, and at 2-hour intervals after each dosing until re-dosing or until the end of the treatment period (at earliest 1:00 a.m. or 2 hours after the last dose, whichever was later). The overall intensity of fireworks was estimated at the same time points.

Primary effectiveness variable: Owner assessment of the effect of study treatment on their dog's signs of fear and anxiety was the primary variable. The owner gave a global assessment of the effect of study treatment on their dog's signs of fear and anxiety on New Year's Eve compared to previous noise events without treatment. The effect of study treatment was assessed once after New Year's Eve (at earliest 1:00 a.m. or 2 hours after the last dose, whichever was later). The dog owner assessed the treatment effect by using the scale presented in Table II.1. Usability of the product was also assessed by the owner at the same time.

Table II.1. Owner Assessment of Treatment Effect on Their Dog's Signs of Noise Aversion

Score	Description
1	Excellent effect: the dog did not react to fireworks with anxious/fearful behavior at all
2	Good effect: the dog's reactions were mild/transient and it could calm down*
3	Some effect: the dog was reacting somewhat less/milder than during previous noise events but it could not calm down*
4	No effect: there was no reduction/change in the dog's reactions compared to previous noise events
5	Worse: the dog's reaction to fireworks were stronger than during previous noise events

*Calm down defined as decrease in the individual anxiety and fear associated behaviors combined with an increase in behaviors associated with relaxed state (such as lying down, accepting food/treats, owner being able to interact with the dog).

Secondary effectiveness variable: The sum of behavior scores of the three most severe signs at 2 hours after each dosing was the main secondary effectiveness variable in this study. The three most severe signs for each dog were defined at screening by the owner based on the experiences with the dog during previous noise exposures. The owner assessed the individual signs and extent of anxiety and fear as the secondary variable using the scale from 0 (none) to 1 (only a few times) through 4 (continuously) of the three of the following eight behaviors: panting, trembling, vocalizing (barking, howling, whining, growling), seeking people (clinging, climbing in lap, pawing at, trying to sit behind or under, following, etc.), pacing (frequent change of place/running around, restlessness), trying to hide (under/behind beds, doors, furniture, dark rooms, etc.), trying to escape, freezing (absence of movement except for respiration), and, if applicable, other specified individual anxiety behaviors. Assessment was made once at the baseline 2 to 5 days before New Year's Eve and then always in relation to study treatment administration (prior, 1-hour post-dosing, and every 2-hours post-dosing). If the dog received only one dose of the study treatment, assessments were conducted at 1-hour and then every 2-hours post-dosing until 1:00 a.m.

Statistical methods:
Primary evaluation of the effectiveness variables included all randomized dogs receiving at least one dose of study treatment. Effectiveness was demonstrated if there was a significant difference between treatment groups with respect to the primary variable. For the primary variable, a generalized linear mixed model with cumulative logit link was used to estimate and test the odds ratio (OR) of tasipimidine versus vehicle control utilizing the GLIMMIX procedure of SAS. The model included treatment as a fixed effect and site and treatment-by-site as

random effects. The significance level was 0.05 (two-sided). Supportively, for the secondary variable, the equality of mean sums of behavior scores between treatments was tested. Sum of behavior scores assessments at 2-hour time points after each dose were analyzed with a repeated measures analyses of covariance (RM-ANCOVA) model utilizing the Mixed procedure of SAS. The model included covariates for baseline behavior score (prior dose values) and intensity of fireworks. Treatment, time, and treatment by time interaction were included as fixed effects and dog, site, and site by treatment interaction as random effects. The significance level was 0.05 (two-sided).

Results:

Primary effectiveness variable: 158 animals (79 treated and 79 controls) were evaluated for effectiveness. For the primary variable, the proportion of dogs with good or excellent treatment effect was higher in dogs administered tasipimidine (43/79, 54%) than in those administered the control (28/79, 35%). See Table II.2 below. The effect of the study treatment on the dogs' signs of anxiety was significant and in favor of tasipimidine (OR 2.59; 95% Confidence Interval (CI) 1.27-5.29, p=0.0118).

Table II.2. Owner Assessment of Treatment Effect/Score by Treatment Group

Treatment Effect	Tasipimidine N = 79	Vehicle N = 79	Total N = 158
Score	**n (%)**	**n (%)**	**n (%)**
1 - Excellent effect	11 (13.9)	7 (8.9)	18 (11.4)
2 - Good effect	32 (40.5)	21 (26.6)	53 (33.5)
3 - Some effect	20 (25.3)	16 (20.3)	36 (22.8)
4 - No effect	16 (20.3)	34 (43.0)	50 (31.6)
5 - Worse	0 (0.0)	1 (1.3)	1 (0.6)

Secondary effectiveness variable: When the mean sum scores of the three most severe signs at 2-hours after each dosing were compared between the two treatment groups, the sum score was significantly different between treatment groups and numerically lower for the dogs administered tasipimidine compared to those administered the control (Estimate -1.20; 95% CI -2.34 to -0.06; p=0.0398).

Of the different types of behaviors, dogs treated with tasipimidine oral solution displayed less panting, seeking people, pacing, trembling, vocalizing, trying to hide, and trying to escape behaviors than those treated with control at 2-hours after the first dose.

Adverse Reactions:
The most common adverse reaction was vomiting, occurring in 6% (5/80) of the dogs administered tasipimidine and in 3% (2/80) of the dogs administered the control. Study treatment was prematurely discontinued due to vomiting in two dogs, one in a dog that had received tasipimidine and in one dog that had received control.

Functional alertness after noise stimulus (dog's ability to stand up and walk): Ten and four of the dogs were unable to walk normally or stand up 2-hours after the first dose in the tasipimidine and control groups, respectively. Of the 30 dogs in the tasipimidine group and 33 dogs in the control group that received a second dose, one tasipimidine treated dog and two dogs receiving control were unable to walk normally or stand up 2-hours after the second dose. Of the four dogs in the tasipimidine group and 15 dogs in the control group that received a third dose, all dogs could stand up and walk normally 2-hours after the third dose. See Adverse Reactions Table II.3 below.

Table II.3. Study No. V3110005 Adverse Reactions - Number (%) of Dogs

Adverse reaction	**Tasipimidine 30 mcg/kg N = 80**	**Vehicle N = 80**
Decreased functional alertness, first dose*	10 (12)	4 (5)
Vomiting	5 (6)	2 (3)
Decreased functional alertness, second dose*	1 (1)	2 (3)
Lethargy	1 (1)	0

*unable to walk normally or stand up 2-hours after dose

Conclusions: The administration of tasipimidine oral solution at a dose of 30 mcg/kg body weight as needed up to 3 times, with a minimum interval of 3 hours between doses, is safe and effective for the treatment of noise aversion in dogs.

Separation Anxiety:

1. Multi-site Field Effectiveness Study

   Title: Tessie® for the Treatment of Separation Anxiety in Dogs. (Study No. V3110008)

   Study Dates: March 2022 to November 2024

   Study Locations:

   Kaarina, Finland
   Espoo, Finland
   Hämeenlinna, Finland
   Raisio, Finland
   Lahti, Finland
   Hyvinkää, Finland
   Ruutana, Finland
   Vantaa, Finland
   Zielonka, Poland
   Warszava, Poland
   Torun, Poland
   Nieuwegein, Netherlands
   La Canada, Spain
   Sevilla, Spain
   Barcelona, Spain
   Madrid, Spain
   Braga, Portugal
   Amares, Portugal
   Wien, AustriaTorno, Portugal
   Vienna, Austria
   Kasten bei Boeheimkirchen, Austria
   Dobersberg, Austria
   Steyr, Austria

Leonstein, Austria

Study Design:

Objective: The primary objective of this study was to confirm clinical safety and effectiveness of Tessie® for the treatment of separation anxiety in dogs.

Study Animals: A total of 224 client owned dogs ranging from 6 months to 14 years of age, and 2 to 73 kg in body weight, were enrolled in the study. One hundred and ninety-nine of the dogs were evaluated for effectiveness: 97 dogs received tasipimidine and 102 dogs received vehicle control. All dogs were healthy or were recorded to have mild systemic disease that was stable, and their diagnosis of separation anxiety was confirmed during the baseline evaluations.

Experimental Design: This field study was a randomized, multi-center, double-blinded, vehicle-controlled study with two parallel groups. Dogs were randomized into two treatment groups in a 1:1 ratio of Tessie® or vehicle control. The study was conducted in accordance with GCP guidelines.

Drug Administration: Dog owners administered the study treatment orally with a syringe 1-hour before they left the dog alone, 3 to 7 days per week, during the 8-week treatment period. For further departures during the day, the second dose could be administered when at least 3-hours had passed from the previous dose. If indicated due to decreased alertness or a start of a rescue treatment, a reduced dose (20 mcg/kg) of study treatment was used when the study treatment was re-introduced after a pause for at least 3 days. Clomipramine administered twice daily at the dose of 1-2 mg/kg, together with a basic behavior modification program, was used as rescue treatment.

Measurements and Observations: Dogs with a diagnosis of separation anxiety were eligible for participation in the study. A veterinarian examined the dog and interviewed the dog owner before starting the baseline period. The owner performed baseline assessments; this included at least two separations and alertness assessments within 30 days prior to the first dose. The owner performed safety assessments throughout the study and performed the effectiveness assessments concerning the dog´s signs and extent of anxiety and fear associated with separation anxiety and overall effect of study treatment for the departures on 3 days per week during the 8-week treatment period. The assessments were made from video recordings that started 10 minutes prior to owner departure and continued for at least 1 hour. After the last treatment, the usability of the product was assessed by the owners.

Primary effectiveness variable: Owner assessment of the effect of study treatment on separation anxiety at week 8 was the primary variable. The signs and extent of separation anxiety of the dog seen on the video recording were compared to dog's signs of separation anxiety during the baseline assessments. The dog owner assessed the treatment effect by using the scale presented in Table II.4.

Table II.4. Owner Assessment of Treatment Effect on Their Dog's Signs of Separation Anxiety

Score	Description
1	Excellent effect: the dog did not show signs of separation anxiety (no new signs and none of those seen at the baseline)
2	Good effect: the dog's signs of separation anxiety were infrequent/mild and it was able to calm down (Fewer signs with lower intensity than seen at the baseline)
3	Some effect: the dogs signs of separation anxiety were infrequent/mild but it was not able to calm down (some reduction in either in the number or extent of signs compared to baseline)
4	No effect: dog is showing all the signs seen at the baseline with the same intensity (no change to baseline)
5	Poor effect: the dog is showing all the signs seen at baseline at higher intensity and/or there are new signs of separation anxiety (worse than baseline)

Secondary effectiveness variable: The overall summary score of the owner assessment of signs and extent of separation anxiety was the main secondary effectiveness variable in this study. For the secondary effectiveness variable, owner departure-related signs and extent of separation anxiety summary scores were created. This was done by summing the scores of the owner assessed individual acute anxiety behavior signs related to owner departures.

The owner assessed the individual signs and extent of separation anxiety as the secondary variable using the scale from 0 (none) to 1 (only a few times) through 4 (continuously) of the following behaviors: vocalizing, restlessness/pacing, destructive/rearranging behavior, salivating, panting, licking, excessive self-grooming/mutilation, freezing (no other movement except respiration)/decreased motor activity (unusually passive), and other specified individual anxiety behaviors. Assessments were made from video recording, twice at the baseline and then three times weekly in relation to dog owner absence. Also, possible observations elsewhere in the home were included.

Statistical methods: Per Protocol sets are the primary analysis sets for the effectiveness analyses. The primary endpoint analysis value was created according to the given rules for the primary and secondary approaches. In the primary approach, analysis value was imputed for the dog if the dog discontinued the study, or the rescue criteria were met. The imputed analysis value for the discontinuations depends on the reason of the discontinuation and whether the rescue criteria were met before or after the discontinuation. Otherwise, the median value of week 8 was used as analysis value. In the secondary approach, the imputation rules are the same, but the rules for rescue criteria are ignored. Thus, the rules for discontinuations are applied regardless of if the rescue criteria were met. Similar imputation rules for the primary and secondary approaches were applied also for the other effectiveness variables.

Effectiveness was demonstrated if there was a statistically significant difference between treatment groups with respect to the primary variable in favor of Tessie®. Primary endpoint was analyzed with a generalized linear mixed model for an ordinal response, with cumulative logit as a link function (i.e. proportional odds cumulative logit model). The model included treatment (fixed), site (random), and treatment by site interaction (random). Results were summarized using model-based odds ratio estimate with 95% confidence interval and p-value.

As a secondary analysis, a binary responder (success/failure) analysis was performed to evaluate improvement (excellent or good effect versus some effect, no effect, or poor effect) in the score using generalized linear mixed model for binary response with logit link function including treatment as a fixed effect, site and treatment by site interaction as random effects.

For the supportive secondary effectiveness variable, descriptive statistics of the overall summary sign score by week including mean, median, standard deviation, etc. were calculated.

Results:
Primary endpoint: One hundred and ninety-nine dogs (97 treated and 102 controls) were evaluated for effectiveness. The owners rated the effect of the study treatment at week 8 positive more often in the Tessie® group compared to the control group. The treatment effect was statistically significant when compared to the control group OR 6.77; 95%, CI 3.21-14.3; p<0.0001.

Secondary variable: A numerical reduction in the mean and median of the overall summary sign scores, as well as the maximum scores, was seen from week 1 onwards in the Tessie® group while those in the control group remained high.

Adverse reactions: The most common adverse reactions after the start of the study treatment were vomiting, lethargy, and diarrhea. The following adverse reactions were reported after start of study treatment:

Table II.5. Study No. V3110008 Adverse Reactions - Number (%) of Dogs

Adverse reaction	Tessie® N = 114	Vehicle Control N = 109
Vomiting	29 (25)	11 (10)
Lethargy	19 (17)	4 (4)
Diarrhea	14 (12)	9 (8)
Elevated liver enzymes	5 (4)	3 (2)
Anxiety	4 (4)	4 (3)
Dermatitis and eczema	4 (4)	3 (2)
Anorexia	3 (3)	7 (6)
Conjunctivitis	3 (3)	1 (1)
Sneezing	2 (2)	1 (1)
Ataxia	2 (2)	1 (1)
Behavioral disorder NOS	1 (1)	3 (3)
Pruritus	1 (1)	3 (3)

NOS-not otherwise specified

Sixteen ARs in 14 dogs led to permanent discontinuation of treatment: Six ARs in four dogs in the control group and 10 ARs in 10 dogs in the Tessie® group. Rescue criteria were met by 64 dogs (60%) in the control group and 18 dogs (17%) in the Tessie® group.

Functional alertness after stimulus (dog's ability to stand up and walk, and overall responsiveness): A higher frequency of the dogs in the Tessie® group were scored "slow to stand up but can walk normally" (48%) and "dog is reluctant to stand up and hesitates to move/is uncoordinated when walking" (9%) compared to dogs in the control group (8% and 0%, respectively). There were no dogs scored "unable to stand up and walk" in either group on Day 1.

Functional alertness (overall responsiveness): A higher frequency of the dogs in the Tessie® group were scored "slow to respond to your call and not as alert as usual" (17%) compared to dogs in the control group (1%). One dog in the tasipimidine group (1%) was scored "unresponsive to your call, abnormally drowsy or sleepy." These dogs were administered a reduced dose of Tessie® (20 mcg/kg) after a washout period.

Conclusions: The administration of Tessie® at a dose of 30 mcg/kg (or if indicated at 20 mcg/kg) body weight as needed up to 2 times per day, with a minimum interval of 3 hours between doses, is safe and effective for the treatment of separation anxiety in dogs.

III. TARGET ANIMAL SAFETY

A. Twenty-Eight Day Margin of Safety Study

Title: Twenty-Eight Day Oral Gavage Toxicity Study in Beagle Dogs. (Study No. 499681)

Study Dates: May 1, 2012 to June 14, 2012

Study Location: Den Bosch, The Netherlands

Study Design:

Objective: To evaluate the safety of tasipimidine at 30, 150, and 510 mcg/kg administered by oral gavage to Beagle dogs.

Study Animals: Twenty-four healthy Beagle dogs aged 7 to 8 months.

Experimental Design: This was a controlled, prospective, and randomized study. Animals were allocated to the treatment groups (0X, 1X, 5X, and 17X), comparable in body weight and age, at the discretion of the study director. No littermates were assigned to the same group. Animals were individually housed. Dogs were group-housed per dose group per sex for at least 3 hours per day, unless contraindicated by study procedures or clinical signs. During the group-housing period, food was not available. The study was performed in accordance with the European Organization for

Economic Co-operation and Development (OECD) Principles of Good Laboratory Practice (GLP).

Table III.1. Treatment Groups for Study No. 499681

Treatment Group	Dose of tasipimidine[1] (mcg/kg/day)	Number & Gender of Dogs
1 (0X)	0, vehicle	6 (3 male, 3 female)
2 (1X)	30	6 (3 male, 3 female)
3 (5X)	150	6 (3 male, 3 female)
4 (17X)	510	6 (3 male, 3 female)

[1]The doses are given as multiples from the single dose 30 mcg/kg.

Drug Administration: Dogs were administered tasipimidine at 0, 30, 150, and 510 mcg/kg once daily by oral gavage for 28 days. Body weight for dosage calculation was the last measurement prior to treatment administration. Treatment was performed approximately 2 hours after feeding. The formulation was an aqueous formulation without excipients, containing tasipimidine sulfate in purified water.

Measurements and Observations: Mortality and viability were checked at least twice daily. Observations for clinical signs were performed 1 to 3 times a day. Special attention was paid to the sedative effects. Body weight and food consumption were followed throughout the study. Ophthalmoscopic examinations, electrocardiogram, indirect blood pressure, complete blood count, blood clotting parameters, serum chemistry, and urinalysis were evaluated before dosing and on Week 4. Toxicokinetic blood sampling was performed on Day 1 and on Week 4 at predose and 0.5, 1, 2, 4, 8, and 24 hours after dosing. The concentration of tasipimidine in dog plasma was quantified using a validated Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) method. Necropsy, organ weights, bone marrow smear, and histopathology were performed at the end of the study.

Statistical Methods: For continuous outcomes measured only once during the study, analysis of variance (ANOVA) was used containing dose, sex, and dose-by-sex interaction. Continuous variables measured at multiple times during the study were analyzed by a repeated measures analysis of covariance, with dose, sex, time, dose-by-sex, sex-by-time, dose-by-time, and dose-by-sex-by-time terms in the model as fixed effects, and animal identified as the subject in the repeated statement. Pre-dose values were used as a covariate. For categorical variables, outcomes deemed clinically relevant, Fisher's exact test was used to evaluate the treated groups versus vehicle control in a pairwise fashion**.**

Results:
At 510 mcg/kg, dogs showed sedation-related effects: moderate to severe lethargy, with postural/motility changes, mild to moderate uncoordinated movements, and/or ptosis on most days of treatment. Furthermore, all dogs showed dryness and/or reddish or pale discoloration of mouth, eye (with purulent discharge from the eye on a few days in individual dogs), ears, and occasionally of the nose. Vomiting and salivation were frequently observed throughout the treatment period. Most clinical signs persisted throughout the day but had mostly resolved before dosing on the next day. There was a slight increase in glutamate dehydrogenase in two females,

occurring in the absence of gross and histopathological liver effects. In addition, triglycerides were slightly increased while the calcium, sodium and potassium were slightly decreased.

At 30 and 150 mcg/kg/day, clinical signs were comparable with those in the 510 mcg/kg group (lethargy, lateral recumbency, vomiting of food, and slight to moderate salivation), although incidence, frequency, and severity were decreased with the lower doses in a dose-dependent manner. There was a dose-dependent decrease in heart rate and blood pressure at all doses. Signs of nausea (salivation, grimace) and incidental vomiting were seen at all doses occasionally.

Tasipimidine was absorbed and eliminated rapidly. On the first day of treatment with the proposed label dose of 30 mcg/kg, the mean ± SD maximum tasipimidine plasma concentration (C_{max}) was 5.3 ±1.22 ng/mL, the mean ± SD time of maximum plasma concentration (t_{max}) was 0.7±0.26 hours, and the terminal half-life was 1.6±0.35 hours. The area under plasma concentration-time curve (AUC0-24h) was 14.2±2.93 ng*h/mL. When dosed at 30-150 mcg/kg/day, the two doses closest to the proposed label dose, there was a less than dose proportional increase (1.8X) in C_{max}, and a dose proportional increase in AUC. There was no accumulation of drug between the first and last dose.

Conclusions: This study supports the safety of tasipimidine in dogs when administered orally at the maximum label dose of 30 mcg/kg. Adverse effects on physiology (lethargy, lateral recumbency, vomiting, salivation, postural changes, and uncoordinated movements) were related to the pharmacology of the drug.

B. Six-month Margin of Safety Study

Title: A 6-Month Target Animal Safety Study With Tessie® by Twice Daily Oral Dosing in Beagle Dogs. (Study No. 20319819)

Study Dates: July 12, 2022, to March 21, 2023

Study Location: Den Bosch, The Netherlands

Study Design:
Objective: To determine the safety of Tessie® When Given Twice Daily, at 3-Hour Intervals, for 6 Months to Beagle Dogs.

Study Animals: Thirty-two healthy Beagle dogs aged 5 to 6 months.

Experimental Design: Animals assigned to the study were stratified by sex, and males and females were separately assigned study positions (cage and treatment group) randomly. After allocation, animals were given a blind identifier (blinded animal number); i.e., blinded animal numbers did not correlate to the dose level. Masking started at randomization. Animals were pair-housed based on sex and treatment group and housed in two rooms by sex. In order to minimize bias, a blinded and a non-blinded database were used to collect in-life study data. The blinded database was used to collect data from observations and measurements (blood pressure, clinical observations, etc.). The unblinded database was used to collect data that could link

the animal to its given treatment, such as dosing data. The study was performed in accordance with the OECD GLP.

Treatment Groups:

Table III.2. Treatment Groups for Study No. 20319819

Treatment Group	Dose of Tessie® (mcg/kg)[1]	Number & Gender of Dogs
1 (0X)	0, vehicle	8 (4 male, 4 female)
2 (1X)	30	8 (4 male, 4 female)
3 (3X)	90	8 (4 male, 4 female)
4 (5X)	150	8 (4 male, 4 female)

[1]Dogs were dosed twice per day, 3 hours apart.

Drug Administration: Dogs were administered Tessie® (final market formulation) at 30, 90, or 150 mcg/kg twice daily (into the mouth/via oral gavage) for 6 months. Dogs in the control group (0X) were administered vehicle oral solution at a volume that matched the 5X group twice daily (into the mouth) for 6 months. The twice daily administrations were separated by 3 hours in all groups.

Measurements and Observations: Mortality was checked at least twice daily. Observations for clinical signs were performed 1 to 5 times a day and special attention was paid to observing sedative effects. Veterinary examinations were performed once monthly. Body weight and food consumption were followed throughout the study. Respiratory rate, electrocardiogram, and indirect blood pressure were evaluated before dosing and 4 times a day on Day 2 and 4 times per day on 1 day of Weeks 4, 13, and 26. Ophthalmoscopic examinations, and sample collection for complete blood count, blood clotting parameters, serum chemistry, and urinalysis evaluation were performed during the pre-treatment period and then during Weeks 4, 13, and 26. Toxicokinetic blood sampling was performed on Week 26 (Day 182) at 0.5, 1.5, 3 (prior to the second daily dose), 3.5, 4.5, 6, 9, and 24 hours after the first daily dose. The concentration of tasipimidine in dog plasma was quantified using a validated LC-MS/MS method. Necropsy, organ weights, bone marrow smear, and histopathology were performed at the end of the study.

Statistical Methods: The experimental unit was the cage. No statistical analysis was conducted due to the small number of experimental units. Descriptive statistics for continuous variables, including the number of experimental units, mean, standard deviation, minimum, and maximum value, were provided by treatment and treatment-by-sex. For continuous variables measured repeatedly, treatment summaries by time and sex-by-time were provided. For categorical variables, frequency summaries were provided by treatment and treatment-by-sex. Variables repeatedly measured were also summarized by time point.

Results:
Dogs in all treated groups administered Tessie® showed dose dependent sedation related effects, including severe ataxia/abnormal gait, lateral recumbency, partly closed eyes, decreased activity, and depression. At 1X, the sedation-related clinical

signs were comparable to the 3X and 5X groups, but the occurrence and severity were lower. In all dogs, signs of sedation resolved prior to dosing on the next day.

At all dose levels, sedation was accompanied by a dose-dependent increase in capillary refill time and dry gums, and a dose-dependent decrease in body temperature, respiratory rate, and heart rate with concomitant changes in electrocardiography parameters with no waveform abnormalities. Salivation was observed regularly before dosing at all dose levels (including control).

In the 3X and 5X dose groups, slight increases in plasma triglycerides, creatine kinase, glutamate dehydrogenase, and urea were seen. In the 5X group, there were also slight increases in plasma alkaline phosphatase and bile acid concentrations. At 5X, irregular heart rate and/or grade II-III heart murmur were noted in one dog starting at the Day 14 veterinary exam.

After 6-month twice daily dosing at 3-hour intervals with the label dose of 30 mcg/kg tasipimidine, the geometric mean ± standard deviation (SD) maximum tasipimidine plasma concentration (C_{max}) after the first dose on Day 182 was 4.35±1.36 ng/mL and the median time to maximum concentration (T_{max}) was 0.5 hours (range: 0.5-1.5 hours). After the second dose on Day 182, the geometric mean ± SD C_{max} and half-life were 5.39±1.46 ng/mL and 3.04±1.14 hours, respectively. The median T_{max} after the second dose on Day 182 was 1.5 (range: 0.5 - 3) hours. The geometric mean ± SD area under the curve from the time of first dosing to the last quantifiable concentration (AUC0-24hours) was 28.5±1.43h*ng/mL. Re-dosing of 30 mcg/kg at 3 hours resulted in a C_{max} that is approximately 24% higher than the first C_{max}. After administering tasipimidine at 0, 30, 90, and 150 mcg/kg twice daily at 3-hour intervals (into the mouth/via oral gavage) for 6 months, C_{max} after the first daily dose of Day 182 increased in an approximate dose proportional manner.

Conclusion: This study supports the safety of Tessie® in dogs when administered orally at the maximum label dose of 30 mcg/kg twice daily with 3-hour intervals. Clinical signs seen at 1X, 3X, and 5X doses were dose-dependent and related to sedation (decreased activity; ataxia; drowsiness; lying on side; partly closed eyes; and decreased heart rate, respiratory rate and body temperature).

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 Tessie®:

Human Safety Warnings:
Not for human use. Keep out of reach of children.

Appropriate precautions should be taken while handling the product. Avoid skin and eye contact.

The product can be absorbed following direct exposure to eyes or mouth. In case of accidental eye exposure, flush with water for 15 minutes. If wearing contact lenses, eyes should be rinsed first, then remove contact lenses and continue rinsing, then seek medical advice if symptoms occur.

In case of skin contact, wash with soap and water. Remove contaminated clothing.

Accidental exposure may cause sedation and changes in blood pressure. In case of accidental exposure, seek medical attention if symptoms occur. Exposure to the product may induce a local or systemic allergic reaction in sensitized individuals.

In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician. Do not drive as sedation and changes in blood pressure may occur.

Note to physician: This product contains an alpha-2 adrenoceptor agonist.

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 (FD&C Act) and 21 CFR part 514. The data demonstrate that Tessie®, when used according to the label, is safe and effective for the conditions of use in the General Information Section above.

A. Marketing Status

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to properly diagnose noise aversion and separation anxiety and to prescribe appropriate treatment.

B. Exclusivity

Tessie®, as approved in our approval letter, qualifies for FIVE years of marketing exclusivity beginning as of the date of our approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(i) of the FD&C Act because this is the first time we are approving this active moiety in a new animal drug application submitted under section 512(b)(1) of the FD&C Act.

C. Patent Information

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