Date of Approval: November 17, 2023

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-580

Bonqat®

(pregabalin oral solution)

Cats

For alleviation of acute anxiety and fear associated with transportation and veterinary visits in cats.

Sponsored by:

Orion Corp.

Executive Summary

Bonqat® (pregabalin oral solution) is approved for the alleviation of acute anxiety and fear associated with transportation and veterinary visits in cats. The drug is administered orally approximately 1.5 hours before the start of the transportation or veterinary visit and can be given on two consecutive days. Pregabalin is a Schedule V controlled substance.

Safety and Effectiveness

The sponsor conducted a two-phase field study in client-owned cats with a history of having anxiety and/or fear when transported by car and during veterinary visits. Enrolled cats were both sexes, ranged in age from 5 months to 15 years, and were a variety of weights and breeds. In the first phase, two doses were evaluated against placebo, and the final dose was selected in a planned interim analysis. The final dose (5 mg/kg) was used in the second phase of the study where cats received either pregabalin at the final dose or placebo.

The study consisted of a pre-screening period (interview and training of the owner), followed by a screening visit (examination by a veterinarian). A treatment visit was conducted by the veterinarian 5 to 10 days after the screening visit, and an end-of-study contact with each owner was performed within 3 to 10 days after the treatment visit. The effectiveness of Bonqat® was based on the cat's anxiety and/or fear when transported in a car (owner's assessment) and during a physical examination at the veterinary clinic (veterinarian's assessment). The assessments were coded on a 5-point ordinal scale, with 1 being an excellent response and 5 being a very poor response. A little over half of cats given Bonqat® at a dose of 5 mg/kg had a good to excellent response during both transportation and the veterinary visit compared to about one-third of cats given placebo. In addition, from the screening visit to the treatment visit, 83 of 108 (77%) cats given Bonqat® at 5 mg/kg showed improvement compared to 46 of 101 (46%) cats given placebo. Adverse reactions related to Bonqat® included mild sedation, ataxia, and lethargy.

The sponsor conducted two margin of safety studies in young, healthy, male and female cats. The cats were administered Bonqat® orally at 0X, 1X, 3X, or 5X the labeled dose for 3 or 6 days. In both studies, treatment was associated with sedation, ataxia, uncoordinated behavior, lethargy, and decreased body temperature in a dose-dependent manner. Treatment was also associated with a lowering of heart rate (bradycardia at higher doses), with some cats having reflexive hypertension and reflex tachycardia.

User Safety

Pregabalin is a Schedule V controlled substance. Therefore, the labeling for Bonqat® contains information about drug abuse, addiction, and diversion. People exposed to pregabalin should seek medical advice and may experience the following symptoms: dizziness, sleepiness, blurred vision, weakness, dry mouth, and difficulty with concentration or attention.

Conclusions

Based on the data submitted by the sponsor for the approval of Bonqat®, the U.S. 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 141-580

B. Sponsor

Orion Corp.
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Drug Labeler Code: 052483

U.S. Agent Name and Address:

James H. Schafer, D.V.M.
Schafer Veterinary Consultants, LLC
800 Helena Court
Fort Collins, CO 80524

C. Proprietary Name

Bonqat®

D. Drug Product Established Name

pregabalin oral solution

E. Pharmacological Category

Ligand of alpha2-delta subunit of voltage-gated calcium channels

F. Dosage Form

Oral Solution

G. Amount of Active Ingredient

Each mL of Bonqat® contains 50 mg pregabalin

H. How Supplied

Bonqat® is packed in a clear glass bottle (containing 2 mL of dosing solution) with a child resistant closure and adapter. The bottle is further packed into a carton with a package insert, client information sheet, and an oral syringe (1 mL).

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

Bonqat® is administered orally as a single dose of 5 mg/kg (0.1mL/kg) approximately 1.5 hours before the start of the transportation or veterinary visit.

Bonqat® can be given on two consecutive days. A small amount of food can be given with the product.

K. Route of Administration

Oral

L. Species/Class(es)

Cats

M. Indication

Bonqat® is indicated for alleviation of acute anxiety and fear associated with transportation and veterinary visits in cats.

II. EFFECTIVENESS

A. Dosage Characterization

Dosage characterization of pregabalin is based on 3 nonclinical studies in laboratory cats and 2 clinical field studies in client-owned cats.

1. Non-clinical laboratory studies

   The results of a non-clinical study that evaluated a range of doses of pregabalin support the conclusion that pregabalin is well tolerated at the dose range of 2-20 mg/kg when given as a single oral dose to healthy conscious laboratory cats. Cats administered higher doses experienced more signs of sedation, lethargy, and ataxia. The dose 5 mg/kg was further investigated in nonclinical studies for formulation development purposes, and to study the effect of food on the pharmacokinetics of pregabalin. Due to the study design, the food effect on the absorption of pregabalin was not fully elaborated. The study results support the conclusion that food decreases the systemic exposure [maximum observed concentration (C_{max}) and area under plasma concentration-time curve from time zero to the last quantifiable time point (AUC_{last})] of pregabalin; however, a small amount of food may not have a substantial effect on absorption.

2. Pilot clinical field study

   A pilot clinical field study with crossover design was conducted in 13 client-owned cats with signs of acute anxiety associated with transportation. The cats were randomized to receive 2 different doses of pregabalin (5 and 10 mg/kg) and

placebo in a randomized order during the first 3 treatment periods. During the 4th treatment period, all cats received pregabalin at an individually adopted dose between 2.5 and 12.5 mg/kg. On each of the four treatment days, cats were placed into a carrier and transported by car. The study results support a treatment effect of pregabalin compared to placebo for alleviation of anxiety and fear associated with transportation in cats. The doses of 2.5 mg/kg and 5 mg/kg were selected for further development.

3. Pivotal clinical field study - Stage 1

   The final dose of pregabalin in cats with acute anxiety and fear associated with transportation and veterinary visits was selected in the first stage of a randomized, double-blind, placebo-controlled, parallel-group, multicenter clinical field study with an adaptive seamless design. Ninety client-owned cats between 5 months and 14 years of age and weighing 1.8-7.6 kg were included in stage 1 of the study. Twenty-eight cats were administered a single dose of 2.5 mg/kg of pregabalin, 31 cats were administered 5 mg/kg of pregabalin, and 31 cats were administered placebo. An interim analysis was conducted by an independent data monitoring committee. Based on the results of the interim analysis, the pregabalin dose of 5 mg/kg was considered to have a good safety profile and was statistically significantly different and superior to both placebo and the 2.5 mg/kg dose. Therefore, the 5 mg/kg dose was selected for further evaluation.

B. Substantial Evidence

Note: ORM-0134357 is an early identifier of Bonqat®

Title: ORM-0134357 Oral Solution for Alleviation of Feline Stress, Anxiety and/or Fear Associated With Travel and Veterinary Visits: A pivotal Clinical Field Study. (Study No. V3120002)

Study dates: September 4, 2018 to November 21, 2019

Study Locations:

Helsinki, Finland	Ballyshannon, Ireland
Raisio, Finland	Drogheda, Ireland
Hämeenlinna, Finland	Tullamore, Ireland
Espoo, Finland	Ardee, Ireland
Frontenhausen, Germany	Amares, Portugal
Sümeg, Hungary	Chaves, Portugal
Szkésfehérvár, Hungary	Vila Verde, Portugal
Paks, Hungary	Pardihó, Portugal
Veszprém, Hungary	Esmoriz, Portugal
Kaposvar, Hungary	Braga, Portugal
Virginia, Ireland	Vila Meã, Portugal

Study Design:

Objective: The primary objectives of this study were to select the optimal dose and to confirm effectiveness of pregabalin oral solution in cats that show signs of anxiety and/or fear during transportation (at least 20 min) and veterinary visits. The secondary objectives of this study were to assess clinical safety of pregabalin, and the usability of the product evaluated by the owner.

Study animals: A total of 243 cats were enrolled to the study. Of the 238 randomized cats, 29 cats received pregabalin at a dose of 2.5 mg/kg, 108 cats received pregabalin at a dose of 5 mg/kg, and 101 cats received placebo (vehicle). The cats were between 5 months and 15 years of age and weighed 1.8 to 10.3 kg. All cats were healthy or had a mild systemic disease that was stable, and had a history of being anxious and/or fearful when transported by a car and during veterinary visits.

Experimental Design: This was a well-controlled, parallel-group, multicenter clinical field study conducted in Europe. Two doses were evaluated against placebo (vehicle) during the first phase of enrollment and the final dose was selected in a planned interim analysis. In the second phase of the study, subjects were enrolled only to the selected dose and placebo groups. The study was conducted according to the principles of Good Clinical Practice (GCP). In the first stage of the study, cats were randomized into three treatment groups in a 1:1:1 ratio of pregabalin at a dose of 2.5 mg/kg, pregabalin at a dose of 5 mg/kg, or placebo. After the interim analysis based on data from the first 90 cats enrolled in the study, the rest of the enrolled cats were randomized into two treatment groups in a 1:1 ratio of pregabalin at a dose of 5 mg/kg or placebo.

Drug administration: Study treatment was administered to the cat at home by the owner. Administration was done orally approximately 1.5 hours before placing the cat into the carrier for transportation to the veterinary clinic. Prior to the screening visit, all cats were administered tap water, and prior to the treatment visit, each cat was administered its randomized treatment to keep both study visits as similar as possible.

Measurements and observations:

Cats with previous history of being anxious and/or fearful when transported by car and during veterinary visits were eligible for the study participation. Additionally, the cats had to have scores of at least 3 on the owner assessment during transportation and the investigator assessment at the clinical examination at the screening visit (see description of the scoring below). The study consisted of a pre-screening period (interview and training of the cat owner), followed by a screening visit with physical examination, baseline assessments, and randomization of eligible cats. A treatment visit was conducted 5-10 days after the screening visit in a similar manner as the screening visit. An end-of-study contact was performed within 3-10 days after the treatment visit. Cat owners video recorded the transportation to the veterinary clinic on the screening and treatment visits. The videos were later studied by an external expert for assessment of the behavior of the cats during transportation.

Treatment outcome was measured using two primary effectiveness endpoints: (1) the owner's assessment of the treatment effect based on the cat's anxiety and/or fear during transportation in a car; and (2) the investigator's assessment of the treatment effect based on the cat's anxiety and/or fear during physical examination at the clinic. These endpoints were multinomial variables coded on a 5-point ordinal scale (see Tables II.1 and II.2). As secondary variables, the owners assessed the ability to place the cat into the carrier; the cat's signs of anxiety and/or fear; and duration of possible effect. Additionally, the owner assessed usability of the product (the level of difficulty to administer the product to their cats).

Table II.1. Owner's Assessment of the Treatment Effect Based on Cat's Stress, Anxiety and/or Fear During the Transportation In a Car

Score	Description
1	Excellent: Cat was calm and quiet during the whole transportation time, did not express signs of stress, anxiety and/or fear.
2	Good: Cat was calm and quiet during most of the transportation time. Transient mild signs of stress, anxiety and/or fear (e.g. occasional vocalization, salivation or locomotion) up to 25% of the transportation time.
3	Fair: Cat showed moderate signs of stress, anxiety and/or fear (e.g. vocalization, salivation, locomotion or other activity in bouts) up to 50% of the transportation time.
4	Poor: Cat showed strong signs of stress, anxiety and/or fear (e.g. vocalization, salivation, locomotion or other activity almost without interruption or in longer, more forceful bouts) up to 75% of the transportation time.
5	Very poor: Cat showed extreme signs of stress, anxiety and/or fear (e.g. vocalization, salivation, locomotion or other activity forcefully and without interruption) for 75-100% of the transportation time.

Table II.2. Investigator's Assessment of the Treatment Effect Based on Cat's Stress, Anxiety and/or Fear During the Clinical Examination at the Clinic

Score	Description
1	Excellent: Clinical examination could be easily performed without resistance or with insignificant resistance (no restraint needed). Cat was compliant and not frozen and did not express signs of stress, anxiety and/or fear.
2	Good: Minor resistance; clinical examination could be performed with the technician minimally restraining the cat by placing a hand on the head or back. Cat was compliant and not frozen and expressed mild signs of stress, anxiety and/or fear.
3	Fair: Moderate resistance or freezing. Cat expressed moderate signs of stress, anxiety and/or fear. Clinical examination could be performed with the veterinary technician using physical restraint involving stabilizing the cat and holding in place. Freezing is defined as a moderately tense body.
4	Poor: Strong resistance or freezing. Cat expressed strong signs of stress, anxiety and/or fear. Clinical examination could be performed without sedation with the veterinary technician more tightly restraining the cat (physically wrapping or scruffing cat). Freezing is defined as a very tense body, e.g. absence of movement except respiration.

Score	Description
5	Very poor: Extremely strong resistance. Cat expressed extreme signs of stress, anxiety and/or fear and responded to the clinical examination with avoidant and/or defensive behavior to an extent that completing the examination required sedation.

For evaluation of safety, the investigators assessed the cat's alertness at the beginning of the clinical examination and the owners assessed the cat's activity and ability to stand up and walk at three timepoints after returning home from the veterinary visit. Additionally, hematology and clinical chemistry laboratory assessments were performed on both screening and treatment visits, and adverse events were recorded throughout the study.

Statistical Methods:

All statistical analyses were performed on the per-protocol data set, consisting of all enrolled cats without any major protocol deviations. Cats that were considered sedated according to predefined criteria in the study protocol were excluded from the analyses. All cats that received study treatment were included in the evaluation of safety. The primary objectives were evaluated by comparison of the 5 mg/kg dose selected in stage 1 against placebo using data collected until the end of stage 2. Both primary variables were analyzed using a generalized linear mixed model, with a cumulative logit link function. The statistical model included treatment as a fixed effect and center and center-by-treatment interaction as random effects. The baseline score was included as a covariate. Hypotheses were tested at two-sided 5% level of significance, and 95% confidence intervals were generated around point estimates. An adjusted global p-value was calculated by combining the results from the two stages. The stage wise p-values were combined using weights determined by the square root of the information fraction (n/N), where n is the stagewise sample size and N is the total sample size.[1,2] This adjustment was used for all analyses that combined the stage wise results.

The multinomial secondary variables were analyzed with a similar model as above. Owner's assessment of signs of anxiety and/or fear (e.g. sum of behavior scores) was analyzed with a repeated measures analyses of covariance (RM-ANCOVA) model. Treatment, time, and treatment-by-time interaction were fixed effects and subject, center, and center-by-treatment interaction were random effects. Estimates for individual time points were generated.

[1] Hung, J., Cui, L. and Wang, S-J. Adaptive Statistical Inference Following Sample Size Modification Based on Interim Review of Effect Size. Journal of Biopharmaceutical Statistics 15(4), 693-706.
[2] Christopher Jennison & Bruce W. Turnbull (2007) Adaptive Seamless Designs: Selection and Prospective Testing of Hypotheses, Journal of Biopharmaceutical Statistics, 17:6, 1135-1161.

All safety variables were summarized by the treatment group using descriptive statistics.

Results:

The pregabalin dose of 5 mg/kg demonstrated a statistically significant treatment effect compared to placebo for both the owner's assessment and the veterinarian's assessment, based on the adjusted global p-values calculated from the two stages ($p < 0.0010$ for both variables). Using data from stages 1 and 2, the estimated odds ratio (OR) for owner's assessment is 4.31 in favor of pregabalin. This means that the odds of observing better outcomes for owner's assessment is more than 4-fold higher in the pregabalin group relative to placebo. Similarly, the OR for investigator's assessment is 3.32 in favor of pregabalin, which means that the odds of observing better outcomes with respect to the investigator's assessment is more than 3-fold higher in the pregabalin group relative to placebo.

These results are illustrated in the distributions of post-treatment owner's and investigator's assessments in Table II.3 and II.4, respectively. Table II.3 shows that the owners assessed cats administered pregabalin at the dose of 5 mg/kg to have excellent or good response during the transportation in 54% of cases; the corresponding proportion in the placebo group is 27% as detailed in Table II.3 below.

Table II.3. Owner's Assessment of Treatment Effect

Score	**Percent of Cats with Each Score**	**Percent of Cats with Each Score**
-	Bonqat®	Placebo (vehicle)
Excellent	19.6	6.3
Good	34.8	20.8
Fair	21.7	28.1
Poor	15.2	30.2
Very Poor	8.7	14.6

The investigators assessed cats administered pregabalin at the dose of 5 mg/kg to have excellent or good effect during the clinical examination for 52% of cases; the corresponding proportion in the placebo group is 30% as detailed in Table II.4 below.

Table II.4. Investigator's Assessment of Treatment Effect

Score	**% of Cats with Each Score**	**% of Cats with Each Score**
-	Bonqat®	Placebo (vehicle)
Excellent	13.0	1.0
Good	39.1	29.2
Fair	31.5	44.8
Poor	10.9	12.5
Very Poor	5.4	12.5

Eighty-three out of 108 (77%) cats in the treatment group (5 mg/kg) showed improvement from screening to treatment visit. Forty-six out of 101 (46%) cats in the placebo group showed improvement from screening to treatment visit.

Twenty-five cats in the treatment group (5 mg/kg) showed no improvement (20) or worsening (5) from screening to treatment visit. Fifty-five cats in the placebo group showed no improvement (48) or worsening (7) from screening to treatment visit.

The secondary effectiveness variable findings are in line with the primary variable results. The treatment effect for the owner's assessment of ability to place the cat into the carrier was significantly different in favor of pregabalin at the dose of 5 mg/kg compared to placebo ($p = 0.0094$). The overall difference in the mean sum of signs of anxiety and/or fear at the treatment visit was also statistically significant in favor of pregabalin at the dose of 5 mg/kg compared to placebo ($p = 0.0148$). Based on the owners' observations, vocalization, panting/intense breathing, activity, resistance, and freezing were the signs with the greatest decrease between the screening and treatment visits in the pregabalin group.

Usability of the product was good, as the majority (approximately 79%) of the cat owners assessed the level of difficulty administering the product as either very easy or easy.

Adverse Reactions: One cat administered pregabalin at the dose of 5 mg/kg was considered to show signs of mild sedation. The owners assessed slightly more cats being very calm/sleeping in the 5 mg/kg group compared to other groups after coming home from the veterinary clinic at the treatment visit compared to the screening visit.

Table II.5. Adverse Reactions

Adverse Reaction	Pregabalin 5 mg/kg N=108	Pregabalin 2.5 mg/kg N=29	Placebo N=101
Ataxia	5 (4.6%)	1 (3.4%)	0
Lethargy	3 (2.8%)	2 (6.9%)	0
Vomiting	2 (1.9%)	0	0
Proprioception abnormality	1 (0.9%)	1 (3.4%)	0
Muscle tremor	1 (0.9%)	0	0
Anorexia	1 (0.9%)	0	0
Weight loss	1 (0.9%)	0	0
Mydriasis	0	1 (3.4%)	0

Conclusion: Pregabalin oral solution at the dose of 5 mg/kg is safe and effective for alleviation of acute anxiety and fear associated with transportation and veterinary visits in cats.

III. TARGET ANIMAL SAFETY

The safety of pregabalin was assessed in two laboratory studies in cats.

A. Margin of Safety Study

Title: ORM-0134357: A Target Animal Safety Study in the Cat. (Study No. 20184090)

Study Dates: March 5, 2019 to December 27, 2019

Study Location: Den Bosch, The Netherlands

Study Design:

Objective: The objective of this study was to provide information on the tolerance of pregabalin 50 mg/mL oral solution (final market formulation) in cats, when given for 6 days.

Study Animals: Thirty-two healthy Domestic shorthair cats (16 male and 16 female) aged 7 months, weighing between 3.6 and 5.2 kg (males) and between 2.7 and 3.4 kg (females).

Experimental Design:

This study was conducted in accordance with the Organisation for Economic Cooperation and Development (OECD) Principles of Good Laboratory Practices (GLP). Cats were housed in three rooms with one cohort in each room. Cats were pair-housed based on sex and treatment group.

Personnel involved in the experimental procedures related to collection of data or samples were masked to treatment. However, the pathologist performing the histopathological evaluation and the statistician performing the statistical analyses were unmasked.

Blocks of 4 cats of the same sex were formed with the cats in each block comparable in age and the mean body weights comparable across blocks. Cats within each block were randomly assigned to the 4 treatment groups. After allocation to groups, the cats were randomly given a blind identifier (blinded animal number), which was not correlated to the treatment group, and which was used for in-life data collection.

Drug Administration: Cats were administered pregabalin at 0, 5, 15 and 25 mg/kg once daily into the mouth for 6 days. The formulation used was the final market formulation, pregabalin 50 mg/mL oral solution. The drug administration was staggered in three cohorts. Control cats were administered a placebo oral solution.

Table III.1. Treatment Groups for Target Animal Safety Study (20184090)

Treatment Group	Dose of pregabalin (mg/kg/day)	Number & Sex of Cats
1 (0X)	0 (negative control)	8 (4 male, 4 female)
2 (1X)	5	8 (4 male, 4 female)
3 (3X)	15	8 (4 male, 4 female)
4 (5X)	25	8 (4 male, 4 female)

Measurements and Observations: Mortality and viability were checked at least twice daily. Observations for clinical signs were performed six times a day during the dosing period. Special attention was paid to the sedative effects. Veterinary physical examination was performed on Day 1 and Day 6 during the dosing period. Body weight and food consumption were followed throughout the study. Rectal body temperature, blood pressure, and heart rate were measured on Day 1 and Day 6. Ophthalmic examination and evaluations for hematology, coagulation parameters, clinical chemistry, and urinalysis were performed before dosing and after the last dose on Day 6 or 7. Plasma exposure levels of pregabalin and its N-methyl metabolite at approximately 24 hours after the last dose were analyzed. 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 by sex and 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:

At 5 mg/kg/day, the observed signs of sedation included: abnormal gait, slight to moderate uncoordinated behavior, decreased activity, slightly limited usage of hind limbs, lying on side, and/or drowsy appearance (i.e., depression, drowsiness, and/or ataxia). Signs were noted at the two-hour post-dosing clinical observation on the first day of treatment. Clinical signs of sedation were resolved at the four-hour clinical observation. One male and one female cat had a decreased body temperature observed two to four hours post-dose, the lowest value was 99°F. Cats had a decrease in heart rate with maximum effect at six hours, but the heart rates stayed within normal range.

At 15 and 25 mg/kg/day, signs of sedation were observed in all cats and included ataxia, lethargy, slightly to moderately limited usage of hind limbs, slight to severe uncoordinated behavior, partially to completely closed eyes, laying on side, dilated pupils, and/or drowsy appearance (i.e., depression, drowsiness, and/or ataxia). On

Day 1, all cats had a decreased body temperature at one or more timepoints, the lowest values were 97.8°F when dosed at 15 mg/kg/day and 98.2°F when dosed at 25 mg/kg/day. One cat dosed at 25 mg/kg/day had a loss of consciousness, abnormal gait, eyes closed, decreased activity, lateral recumbency, sedation, salivation, vomiting, decreased body temperature, and uncoordinated behavior. This cat recovered by the four-hour observation. Directly after dosing, slight to severe salivation was observed in multiple cats on one or more days. Cats had a decreased heart rate with maximum effect at two to six hours; some heart rates were bradycardic at 120-130 bpm. Some cats responded to the bradycardia with a reflexive hypertension. The majority of cats maintained a normal blood pressure. Most adverse observations resolved by eight hours after treatment administration.

The mean plasma concentrations of pregabalin and N-methyl pregabalin on Day 7 generally increased with increasing doses. After six-days of dosing at 5, 15 and 25 mg/kg/day, the mean plasma concentrations of pregabalin were 2.7, 7.7, and 12.8 µg/mL, respectively.

Conclusions: This study supports the safe use of Bonqat® (pregabalin oral solution) in cats when administered orally at the label dose of 5 mg/kg for one to two doses. All dose levels were associated with ataxia, uncoordinated behavior, lethargy, limited usage of hind limbs, lying on side, decreased body temperature, and sedated appearance in a dose-dependent severity and duration of signs. Treatment with Bonqat® was also associated with a lowering of heart rate (bradycardia at higher doses) with a maximum effect at two to six hours post-dose. Some cats had a reflexive hypertension but the majority maintained a normal blood pressure.

B. Target Animal Safety Study

Title: Pregabalin: A 3-Day Target Animal Safety Study in the Cat. (Study No. 20305603)

Study Dates: August 19, 2021 to January 7, 2022

Study Location: Den Bosch, The Netherlands

Study Design:

Objective: The objective of this target animal safety study was to provide information on the tolerance of pregabalin 50 mg/mL oral solution (final market formulation) in cats, when given for 3 days.

Study Animals: Thirty-two healthy Domestic shorthair cats aged 1 to 3 years (16 males and 16 females). Males weighed between 4.4 and 5.9 kg and females weighed between 2.6 and 4.1 kg.

Experimental Design:

This study was conducted in accordance with OECD Principles of GLP. Cats were socially housed (free roaming) during the acclimatization period but individually housed during the pre-treatment and dosing periods. Personnel involved in the

experimental procedures related to collection of data were masked to treatment. However, the statistician(s) performing the statistical analyses were unmasked.

Blocks of 4 cats of the same sex were formed, the cats in each block being comparable in age and body weight. Cats within each block were randomly assigned to 1 of the 4 treatment groups. After allocation to groups, the cats were randomly given a blind identifier (blinded animal number), which was not correlated to the treatment group, and which was used for in-life data collection.

Drug Administration: Cats were administered pregabalin at 0, 5, 15 and 25 mg/kg once daily into the mouth for 3 days. The formulation used was the final market formulation, pregabalin 50 mg/mL oral solution. The drug administration was staggered in 4 cohorts with each cohort including 1 male block and 1 female block. Each cohort was initiated with drug administration 7 days apart. Control cats were administered a placebo oral solution.

Table III.2. Treatment Groups for Target Animal Safety Study (20305603)

Treatment Group	Dose of pregabalin (mg/kg/day)	Number & Sex of Cats
1 (0X)	0 (negative control)	8 (4 male, 4 female)
2 (1X)	5	8 (4 male, 4 female)
3 (3X)	15	8 (4 male, 4 female)
4 (5X)	25	8 (4 male, 4 female)

Measurements and Observations: Mortality and viability were checked at least twice daily. Observations for clinical signs (including grading of sedation level) were performed at least five times daily up to 12 hours after dosing. Veterinary physical examination was performed before and at the end of the dosing period. Rectal body temperature, respiratory rate, blood pressure and heart rate were measured five times daily up to 8 hours after dosing. Body weight was measured before and after the dosing period. No necropsy was performed at the end of the study.

Statistical method: The experimental unit was the individual animal. Body weight was analyzed using Analysis of Covariance (ANCOVA) models, which included treatment, sex, and the treatment*sex interaction as fixed effects and cohort as a random effect. The last pre-treatment body weight was included as a covariate. Blood pressure, heart rate, respiratory rate, and body temperature were analyzed by Repeated Measures Analysis of Covariance (RMANCOVA) model, which included treatment, hour, sex, treatment*sex, treatment*hour, hour*sex, and treatment*sex*hour interaction as fixed effects, and cohort as a random effect. The last available pre-treatment value was included as a covariate.

Results:

At 5 mg/kg/day, the signs of sedation observed in 6 of 8 cats included: abnormal gait, decreased body temperature, decreased respiratory rate, and/or lethargy. These signs were observed for between one and six hours after dosing on the first day of treatment. On Day 2 at six hours post-dose, one cat had muscle tremors that resolved without treatment by the 8-hour observation. Three cats experienced bradycardia (120-128 bpm) with maximum effect from two to six hours post-dose, but the heart rates remained within the normal range for the other five cats.

At 15 and 25 mg/kg/day, the signs of sedation observed in all cats included: ataxia, decreased body temperature, lethargy, uncoordinated behavior, decreased respiratory rate, and/or they were cold to the touch. The signs of sedation were observed for 12 hours after dosing. One cat in the 15 mg/kg/day dose group had muscle tremors at four hours post-dose as well as ataxia, lethargy, decreased body temperature, and a decrease in heart rate. Cats had a decrease in heart rate with maximum effect at two to six hours post-dose; a few heart rates were bradycardic at 106-122 bpm. The majority of cats maintained a normal blood pressure, but a few cats responded to the bradycardia with a reflex hypertension. One cat in the 15 mg/kg/day dose group had bradycardia with reflex hypertension at two hours post-dose followed by a reflex tachycardia at six- and eight-hours post-dose.

Conclusions: This study further supports the safe use of Bonqat® (pregabalin oral solution) in cats when administered orally at the label dose of 5 mg/kg. Treatment is associated with sedation, ataxia, uncoordinated behavior, lethargy, decreased body temperature and decreased respiratory rate in a dose dependent manner. Two cats had transient muscle tremors. Bonqat® was also associated with a lowering of heart rate (bradycardia at higher doses) noted up to six hours post-dose. A few cats had bradycardia with reflexive hypertension and few cats had reflex tachycardia after bradycardia.

IV. HUMAN FOOD SAFETY

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

V. USER SAFETY

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

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

Appropriate precautions should be taken while handling Bonqat®. Avoid skin contact, eye contact, or contact with mucus membranes.

Symptoms of exposure to pregabalin include dizziness, sleepiness, blurred vision, weakness, dry mouth, and difficulty with concentration or attention.

In case of accidental eye or mucosal exposure, flush with water for 15 minutes. If wearing contact lenses, eyes should be rinsed first, then remove contact lenses and continue rinsing. Seek medical advice if symptoms occur.

In case of skin contact, wash with soap and water immediately. Remove contaminated clothing. Seek medical advice if symptoms occur.

In case of accidental ingestion, seek medical advice if symptoms occur. Do not drive as sleepiness may occur. In case of ingestion by a child, seek medical attention immediately. Show the package leaflet or the label to the physician.

Drug Abuse, Addiction, and Diversion
Controlled Substance:
Bonqat® contains pregabalin, a Schedule V controlled substance.

Abuse: Abuse is defined as the intentional, non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. Pregabalin is not known to be active at receptor sites associated with drugs of abuse. However, pregabalin is associated with drug liking and is known to be misused and abused in the community, particularly in combination with opioids. Consider the potential risks of misuse or abuse before prescribing this product. Signs of pregabalin misuse or abuse include drug seeking behavior.

Pregabalin should be handled appropriately to minimize the risk of diversion, including restriction of access, the use of accounting procedures, and proper disposal methods, as appropriate to the clinical setting and as required by law.

Note to physician: Bonqat® contains pregabalin.

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 Bonqat®, 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 because it is a DEA Schedule Class V drug with a potential for human abuse. Furthermore, adequate directions for lay use cannot be written because professional expertise is required to monitor the safe use of the product, including proper dosing and administration.

B. Exclusivity

Bonqat®, 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.