Date of Approval: November 19, 2015

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-456

SILEO

(dexmedetomidine oromucosal gel)

Dogs

For the treatment of noise aversion in dogs.

Sponsored by:

Orion Corp.

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I. GENERAL INFORMATION

A. File Number

NADA 141-456

B. Sponsor

Orion Corp.,
Orionintie 1,
02200 Espoo,
Finland

Drug Labeler Code: 052483

US Agent:
Dr. Douglass Oeller
Douglass Oeller Consulting, Inc.
13017 Wisteria Drive, Number 134
Germantown, MD, 20874

C. Proprietary Name

SILEO

D. Established Name

Dexmedetomidine oromucosal gel

E. Pharmacological Category

Alpha-2 adrenoceptor agonist

F. Dosage Form

Oromucosal gel

G. Amount of Active Ingredient

Each mL of SILEO contains 0.09 mg dexmedetomidine (equivalent to 0.1 mg dexmedetomidine hydrochloride)

H. How Supplied

3 mL, prefilled multidose oral syringe

I. Dispensing Status

Rx

J. Dosage Regimen

SILEO is administered onto the oral mucosa between the dog's cheek and gum at the dose of 125 mcg/m^2. The gel is absorbed through the oral mucosa and therefore it should NOT be swallowed. If the gel is swallowed, the product may not be effective. If the gel is swallowed, do not repeat the dose for at least two hours.

The first dose of SILEO should be administered approximately 30-60 minutes before the fear and/or anxiety-eliciting noise stimulus, immediately after the dog shows first signs of anxiety or fear related to noise, or when the owner detects a typical noise stimulus (e.g. sound of fireworks) eliciting anxiety or fear in the dog. If the noise event lasts longer than 2-3 hours and the dog's signs of fear and/or anxiety reappear, another dose may need to be given. To avoid overdosing, there should always be at least two hours' pause between dosages. No more than 5 doses can be given during one noise event.

K. Route of Administration

Oromucosal

L. Species/Class

Dog

M. Indication

SILEO is indicated for the treatment of noise aversion in dogs.

II. EFFECTIVENESS

A. Dosage Characterization

1. Pilot non-clinical laboratory studies

The results of 3 pilot non-clinical laboratory studies in healthy Beagle dogs indicated that while a 57 mcg/m^2 dose of dexmedetomidine showed only a transient effect, 125 mcg/m^2 and 250 mcg/m^2 doses were appropriate for further examination in a clinical field study setting. Both doses, repeated up to 5 times at 2-hour intervals, did not sedate dogs excessively and did not cause safety concerns. Reversible changes in bradycardia, hypothermia, and blood pressure were seen in non-anxious/fearful dogs in the 125 mcg/m^2 and 250 mcg/m^2 dosing groups in the studies. Dexmedetomidine was absorbed from the mucosa of dogs and had maximum plasma concentrations 45-60 minutes after a single dose.

2. Pilot field study

Dexmedetomidine oromucosal gel was evaluated at doses of 125 or 250 mcg/m^2 against a vehicle control gel in a pilot field study. The study included 36 client-owned male and female pure and mixed breed dogs, between 2 and 11 years of age and weighing between 4 and 52 kg. All dogs were healthy or had stable systemic disease, and had in previous years demonstrated behaviors associated with acute noise aversion to fireworks.

The study dogs were randomized to receive their first dexmedetomidine or control dose pre-emptively/as soon as the dog demonstrated behaviors consistent with noise aversion due to fireworks on New Year's Eve. Examples of behaviors include whining, trembling, hiding, or attempts to escape. The dog could be re-dosed up to 4 times as soon as it began demonstrating the behaviors again, but not sooner than 2 hours after the previous dose. Owners assessed the effectiveness of the study treatment on controlling exhibited behaviors consistent with acute noise aversion compared with behaviors in previous years, rating the overall effectiveness as worse, none, some, or good effect at least 3 hours after the last dose.

The most common adverse reaction was sedation, which occurred in 2 dogs in the 125 mcg/m^2 dose group and in 4 dogs in the 250 mcg/m^2 dose group. Nearly 50% of the dogs in both dexmedetomidine groups had pale mucous membranes 1 hour after the dosing. This effect was transient and resolved before the second and third doses.

Table 1. Adverse Reactions

Adverse Reaction	Number of Dogs Control n=12	Number of Dogs Dexmedetomidine 125 mcg/m^2 n=12	Number of Dogs Dexmedetomidine 250 mcg/m^2 n=12
Sedation	0	2	4
Lack of efficacy	4	0	1
Urinary incontinence	0	1	1
Emesis	0	2	0
Head tremor	0	0	1
Inappropriate urination	0	1	0
Ataxia	0	0	1
Mydriasis	0	0	1
Anxiety disorder	0	0	1
Tachypnea	1	0	0
Lethargy	1	0	0
Tachycardia	1	0	0

Both dexmedetomidine doses (125 and 250 mcg/m^2) were effective in the alleviation of behaviors associated with noise aversion; however, the 125 mcg/m^2 dose exerted acceptable effectiveness while resulting in fewer adverse reactions, especially those related to sedation. Therefore, the 125 mcg/m^2 dose was chosen for further evaluation in the pivotal clinical field study.

B. Substantial Evidence:

1. Field study

a. Title: Dexmedetomidine oromucosal gel for alleviation of canine acute anxiety and fear associated with noise (fireworks), a pivotal study (Study no. V3005025)

b. Investigators:

Sari Jalomäki, DVM - Helsinki, Finland
Ralph Agatha, DVM - Wetter, Germany
Helmut Pinsenschaum, DVM - Münchsteinach, Germany
Milla Lehtinen, DVM - Espoo Finland
Josef Beisl, DVM - Frontenhausen, Germany
Klaus Renner, DVM - Wassenberg, Germany
Eva Einola-Koponen, DVM - Turku, Finland
Andreas Böhm, DVM - Bremen, Germany
Bernd Schulze Zumloh, DVM - Erftstadt-Lechenich, Germany
Iris Rastas, DVM - Kaarina, Finland
Dagmar Moder, DVM - Steingaden, Germany
Gundula Beckmann, DVM - Bremen, Germany
Eduard Abele, DVM - Freising, Germany
Stefanie Poller, DVM - Freilassing, Germany

c. General Study Design

(1) Objective: Confirm the effectiveness of 125 mg/m^2 of dexmedetomidine oromucosal gel for alleviation of behaviors associated with acute noise (fireworks) aversion in client-owned dogs. Other objectives included the evaluation of ease of administration, local tolerance, observational and functional alertness level, and adverse reactions.

(2) Study Animals: A total of 187 client-owned, male and female, pure and mixed breed dogs were randomized in the study. A total of 182 received study treatment: 89 dogs received 125 mg/m^2 of dexmedetomidine oromucosal gel and 93 dogs received vehicle gel. The age of the dogs ranged between 2 and 17 years and body weight ranged between 4 and 67 kg. All dogs were healthy or had stable systemic disease, and had in previous years suffered from acute fear or anxiety due to fireworks.

(3) Drug Administration: The test article was an oromucosal gel containing 0.1 mg dexmedetomidine hydrochloride/mL in an oral syringe. The control was an oromucosal gel containing the same inert excipients without dexmedetomidine. Feeding was not restricted during the study. The first dose (dexmedetomidine or control) was administered before or as soon as the dog first showed noise aversion behaviors. Re-dosing could be performed as soon as the dog again demonstrated noise aversion behaviors, but at least 2 hours after the previous dose, to allow time to assess observable effects of treatment and to avoid

potential cumulative effects of dexmedetomidine. In this study, when owners gave additional doses they used new dosing syringes.

(4) Measurements and Observations: A veterinarian examined the dog and interviewed the dog owner within 4 weeks of the baseline assessments. The owner performed the baseline assessments 2 days before New Year's Eve. The owner performed the effectiveness, safety, and product usability assessments on New Year's Eve or the following day. The owner visited the veterinary clinic and/or was contacted by the veterinary clinic personnel by phone during the first 2 weeks of January.

There were 2 co-primary effectiveness endpoints evaluated in the study. The first co-primary variable was the overall effect of study treatment on noise aversion behaviors in dogs in response to fireworks on New Year's Eve compared with the reactions to fireworks in previous years without treatment. The second co-primary variable was the sum of behavior scores, measured 1 hour after each dose, over the treatment period.

For the first co-primary variable, the dog owner rated the overall effect of study treatment on behavior of the dog at least 2 hours after the last dose compared to previous years without treatment. The dog owner assessed the treatment effect by using the scale presented in the following table.

Table 2. Owner assessment of the treatment effect on the behavior of dogs

Excellent Effect	The dog does not react to fireworks with anxious/fearful behavior at all
Good Effect	The dog's reactions are mild and it can calm down
Some Effect	The dog is reacting somewhat less/milder than in previous year(s) but it cannot calm down
No Effect	There is no reduction/change in the dog's reactions compared to previous year(s)
Worse Effect	The dog's reaction to fireworks is stronger than in previous year(s)

For the second co-primary variable, the dog owner assessed the extent (none; only a few times; some of the time; most of the time; continuously, scaled 0 to 4, respectively) of the following 12 behavioral signs: panting, trembling, vocalizing (any kind of vocalizing including whining, barking, growling, howling, etc.), pacing (frequent change of place/running around, restlessness), seeking people (clinging, climbing in lap, pawing at, trying to sit behind or under, following), trying to hide (under/behind beds, doors, furniture, dark rooms), trying to escape, freezing (absence of movement except for respiration), refuses to eat food/treats, inappropriate urination (a housetrained dog urinates indoors or does not urinate when outside), inappropriate defecation (a

housetrained dog defecates indoors), and salivating (theoretical maximum sum for a dog/timepoint was 48).

Safety was assessed by recording the local tolerance, observational and functional alertness level, and adverse reactions.

(5) Statistical methods: Effectiveness was demonstrated if there was a significant difference between treatment groups with respect to both co-primary endpoints.

The first co-primary variable was analyzed using a generalized linear model with a cumulative logit link function. The model included treatment as a fixed effect and center and the treatment-by-center interaction as random effects.

The second co-primary variable was analyzed using a repeated measures analysis of covariance with treatment, dose and the treatment-by-dose interaction as fixed effect and subject, center and the treatment-by-center interaction as random effects. Data from time points when dogs presented signs of potential sedation in functional alertness assessment 1 hour after dosing were excluded from the primary analysis.

d. Results: 144 animals (71 treated and 73 control) were evaluated for effectiveness.

For the first co-primary endpoint, the proportion of dogs with good or excellent treatment effect was higher in dogs treated with dexmedetomidine oromucosal gel (53/71 dogs) than in those administered control (24/73 dogs). The proportion of dogs with some, no, or worse effect was higher in dogs administered control (49/73 dogs) than in those treated with dexmedetomidine (18/71 dogs). Refer to Table 3. below.

Table 3. Owner assessment of treatment effect/score by treatment group

Treatment Effect	Dexmedetomidine N=71 n (%)	Control N=73 n (%)	Total N=144 n (%)
1 - Excellent Effect	12 (16.9)	8 (11)	20 (13.9)
2 - Good Effect	41 (57.7)	16 (21.9)	57 (39.6)
3 - Some Effect	7 (9.9)	14 (19.1)	21 (14.6)
4 - No Effect	8 (11.2)	32 (43.8)	40 (27.7)
5 - Worse	3 (4.2)	3 (4)	6 (4.2)

There was a statistically significant difference ($p<0.0001$) between dexmedetomidine and control in favor of dexmedetomidine. The odds ratio was 5.5876, with 95% confidence interval (2.7635, 11.2976).

For the second co-primary variable, the mean sum of behavior scores over the treatment period was significantly different between dexmedetomidine and control ($p=0.0069$). The mean score was lower (better) for the

dexmedetomidine oromucosal gel treated group than for the control group (LSMeans: 4.9661, 7.2456 respectively). Refer to Table 4 below.

Table 4. Mean behavioral sum scores by treatment and time point

Dosing Time Point	Dexmedetomidine Sum of Behavior Scores (mean/number of animals)	Placebo Sum of Behavior Scores (mean/number of animals)
Screening	18.75/71	19.01/73
Prior to dose 1	5.04/71	4.96/73
1 hr post-dose 1	3.75/68	4.72/71
Prior to dose 2	7.93/68	9.11/70
1 hr post-dose 2	4.21/52	9.10/60
Prior to dose 3	8.26/38	17.5/44
1 hr post-dose 3	6.35/34	11.0/39
Prior to dose 4	6.92/12	12.95/21
1 hr post-dose 4	5.42/12	12.7/21

Of the different types of behavior, dogs treated with dexmedetomidine oromucosal gel displayed less panting, trembling and trying to hide than those treated with control.

No signs of excessive sedation were observed in the dexmedetomidine oromucosal gel treatment group when the observational and functional alertness of the dogs was evaluated (dogs were evaluated 1 hour after dosing and every 2 hours post-dosing until re-dosing or until the end of treatment period).

Most owners (85%) considered administration of the product to be very easy or quite easy and 15% of the owners reported it to be somewhat difficult or very difficult to administer.

Dexmedetomidine oromucosal gel was well tolerated. Local tolerance was assessed by observation of the color of the oral mucosa before and 2 hours after each dosing. Pale mucous membranes were observed more frequently in dogs treated with dexmedetomidine oromucosal gel than in dogs administered control. In most cases, the effect was transient, and no adverse reactions due to mucosal irritation were reported.

e. Adverse Reactions: The most common adverse reaction was emesis, which occurred in 4 dogs in the dexmedetomidine oromucosal gel group and in 1 dog in the control group. Sedation and drowsiness led to reduction of the dose in 1 dog in the dexmedetomidine oromucosal gel group.

Table 5. Adverse reactions [Number (%) of dogs]

Adverse Reaction	Control N = 93	Dexmedetomidine N = 89
Emesis	1 (1.1)	4 (4.5)
Gastroenteritis	0	1 (1.1)
Periorbital edema	0	1 (1.1)
Drowsiness	0	1 (1.1)
Sedation	0	1 (1.1)

f. Conclusions: The administration of 125 mcg/m^2 of dexmedetomidine oromucosal gel as needed up to 5 times, with a minimum interval of 2 hours between doses, is safe and effective for alleviation of acute noise aversion in dogs.

2. Usability study

A study was conducted to assess the ability of dog owners to correctly administer a predetermined volume of gel with the SILEO dosing syringe. The study was conducted at two veterinary clinics in the United States and did not involve the use of animals. The study is entitled "Usability evaluation to determine whether dog owners can select the correct dose repeatedly from a Sileo syringe." The primary objective of the study was to determine whether dog owners could correctly use the newly designed syringe, specifically to correctly eject a predetermined volume of gel. In addition, the general usability and user friendliness of the product were assessed. Of 60 subjects who completed the study, 55 subjects (92%) were able to repeatedly eject the correct volume of gel. Over 90% of the subjects assessed the usability of the syringe to be 'easy' or 'very easy' to eject the correct volume of gel, and none of the subjects assessed it to be 'very difficult.' The study did not assess accuracy or ease of correct dose administration to actual dogs. In conclusion, this study confirmed that dog owners are reliably able to prepare the SILEO dosing syringe and eject the correct volume of gel from the dosing syringe for a specified dose.

III. TARGET ANIMAL SAFETY

A. Safety of Dexmedetomidine

The safety of dexmedetomidine in dogs has been demonstrated in the target animal safety study of DEXDOMITOR 0.5 mg/mL sterile injectable solution (NADA 141-267). The existing safety margin demonstrated in the target animal safety study of dexmedetomidine injection is not exceeded by the use of the SILEO oromucosal gel formulation as prescribed. On average the bioavailability of dexmedetomidine after oromucosal administration is 28%.

A target animal safety study of dexmedetomidine hydrochloride sterile injectable (DEXDOMITOR) was conducted at doses of 375, 1125, and 1875 mcg/m^2

administered once daily intravenously (IV), or 500, 1500, and 2500 mcg/m^2 administered once daily intramuscularly (IM), on three consecutive days. Dexmedetomidine was well tolerated in the study even at the high dose levels, and adverse effects on physiology were related to the pharmacology of the drug. There were no toxicological effects on body weight, clinical variables, gross or microscopic pathology. Refer to the FOI summary for NADA 141-267 for additional details.

IV. HUMAN FOOD SAFETY

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

V. USER SAFETY

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

WARNINGS:
Human Safety: Not for human use. Keep out of reach of children.
Avoid using product if pregnant, as exposure may induce uterine contractions and/or decrease fetal blood pressure.

SILEO can be absorbed following direct exposure to skin, 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 immediately.

Appropriate precautions should be taken while handling and using filled syringes. Impermeable gloves should be worn when administering SILEO or when coming in contact with the dog's mouth after application. If your skin is damaged, dexmedetomidine can be absorbed into your body. 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 immediately. Exposure to the product may induce a local or systemic allergic reaction in sensitized individuals.

The safety data sheet (SDS) contains more detailed occupational safety information. To report adverse reactions in users or to obtain a copy of the SDS for this product call XXXX.

Note to physician: This product contains an alpha-2 adrenergic 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 SILEO, when used according to the label, is safe and effective for the treatment of noise aversion in dogs.

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 monitor the safe use of the product, including proper dosing and administration of the product.

B. Exclusivity

SILEO, as approved in our approval letter, qualifies for THREE years of marketing exclusivity beginning as the date of our approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(ii) of the FD&C Act, because the sponsor submitted an original NADA that contains new studies that demonstrate safety and effectiveness of SILEO.

C. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.