

Date of Approval: June 15, 2020

FREEDOM OF INFORMATION SUMMARY
ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-534

CLEVOR®

Ropinirole ophthalmic solution

Dogs

For the induction of vomiting in dogs

Sponsored by:

Orion Corp.

Table of Contents

I. GENERAL INFORMATION	3
II. EFFECTIVENESS	5
A. Dosage Characterization	5
B. Substantial Evidence	6
III. TARGET ANIMAL SAFETY	12
A. Margin of Safety Study.....	12
B. Studies to Address Protracted Vomiting.....	15
IV. USER SAFETY	16
V. AGENCY CONCLUSIONS	16
A. Marketing Status.....	16
B. Exclusivity.....	17
C. Patent Information.....	17

I. GENERAL INFORMATION

A. File Number

NADA 141-534

B. Sponsor

Orion Corp.,
Orionintie 1
02200 Espoo, Finland

Drug Labeler Code: 052483

U.S. Agent Name and Address:
James H. Schafer, DVM
Schafer Veterinary Consultants, LLC
800 Helena Court
Fort Collins, CO 80524

C. Proprietary Name

CLEVOR®

D. Drug Product Established Name

Ropinirole ophthalmic solution

E. Pharmacological Category

Emetic, dopamine agonist

F. Dosage Form

Ophthalmic Solution

G. Amount of Active Ingredient

Each mL contains 30 mg of ropinirole (equivalent to 34.2 mg ropinirole hydrochloride)

H. How Supplied

0.3 mL, prefilled single dose dropper. Each dropper contains 9 mg ropinirole. Each dropper is packaged in an individual aluminum foil laminate pouch. Package sizes: Single package of 1 unit-dose dropper and multipackage of 5 unit-dose droppers.

I. Dispensing Status

Rx

J. Dosage Regimen

Administer the appropriate number of eye drops topically according to Table 1. The number of eye drops administered corresponding to body weight results in a target dose of 3.75 mg/m² (dose band 2.7 - 5.4 mg/m²). If the dog does not vomit within 20 minutes of the first dose, then a second dose may be administered.

Table 1. Dose Administration

Body weight in kilograms	Body weight in pounds	Total number of eye drops	Example administration
1.8-5	4-11.1	1	1 drop into either left or right eye
5.1-10	11.2-22.1	2	1 drop each eye
10.1-20	22.2-44.1	3	2 drops in one eye and 1 drop in the other eye
20.1-35	44.2-77.2	4	2 drops in each eye
35.1-60	77.3-132.3	6	An initial dose of 2 drops in each eye, followed 2 minutes later by 1 drop in each eye
60.1-100	132.4-220.5	8	An initial dose of 2 drops in each eye, followed 2 minutes later by 2 drops in each eye

K. Route of Administration

Ophthalmic

L. Species/Class

Dogs

M. Indication

For the induction of vomiting in dogs

II. EFFECTIVENESS

The effectiveness of CLEVOR[®] was demonstrated in one adequate and well-controlled clinical field study described below (II.B. Substantial Evidence). CLEVOR[®] was administered to 100 client-owned dogs. This study demonstrated that CLEVOR[®] is effective for the induction of vomiting in dogs, as 95% of dogs in the CLEVOR[®] group vomited within 30 minutes. Eighty-six percent of dogs in the CLEVOR[®] group vomited after the first dose, and 14% needed a second dose at 20 minutes. CLEVOR[®] is a dopamine agonist that is administered in the eye. The observed adverse reactions were either related to local ocular irritation because of the route of administration or systemic effects related to the dopamine agonist drug class. The most common adverse reactions were local ocular irritation, including conjunctival hyperemia, protrusion of the third eyelid, conjunctival discharge, and blepharospasm; and systemic effects including lethargy, tachycardia and prolonged vomiting. Eight dogs had sporadic vomiting episodes for a period over an hour. Five of these dogs were administered an antiemetic, metoclopramide, to stop the protracted vomiting. During development, ropinirole ophthalmic solution was also referred to as ORM-145704.

A. Dosage Characterization

The dose of 3.75 mg/m² administered as a topical ophthalmic solution according to the dosing table resulting in a dose band of 2.7 - 5.4 mg/m² was selected based on the results of the following pilot studies.

Pilot Laboratory Studies:

Two pilot laboratory studies evaluated the ophthalmic administration of ropinirole solution (not commercial formulation) at a dose range of 1.0 - 4.5 mg/m² to induce vomiting in 13 healthy Beagle dogs. Emesis was induced in all dogs within 12 minutes of administration. Transient observations after administration included lethargy, local irritation of the eyes, and increase in heart rate.

Pilot Field Studies:

One pilot field study was conducted in 20 healthy male and female dogs of pure and mixed breeds between 1 and 15 years old and weighing 14 - 32 kg. Escalating doses of ropinirole 30 mg/mL solution (not commercial formulation) were administered at weekly intervals as approximately 30 µL sized drops (1, 2, and 4 drops) in the eyes of the dogs. A single dose of ropinirole was administered once a week. If a dog vomited within 10 minutes of administration, no re-dose was administered. If a dog did not vomit within 10 minutes after administration, vomiting had not persisted longer than 45 minutes, or the dog had not presented any clinically relevant adverse events, then the dog continued to the higher dose level a week later. An increasing dose of ropinirole correlated with increased probability of vomiting and a shorter time to first vomiting episode. The ropinirole doses (1 - 4 drops) administered during the study corresponded to doses of 0.9 - 5.5 mg/m². A minimum dose of 2.5 mg/m² was selected based on the induction of vomiting within 20 minutes of ropinirole administration during the study.

One additional study was conducted in 30 client-owned pure bred dogs between 11 months and 9 years old and weighing either between 2.5 - 4 kg (small dogs) or 40 - 77 kg (large dogs). Two concentrations (30 and 50 mg/mL) of ropinirole solution (not commercial formulation) were used. The dogs received a number of

drops in the eyes based on body weight resulting in a dose band of 2.6 - 4.5 mg/m². Twenty-eight of the 30 dogs vomited within 17 minutes of initial administration of ropinirole and the remaining two dogs vomited after re-dosing.

The target dose of 3.75 mg/m² (dose band 2.7 - 5.4 mg/m²) of ropinirole ophthalmic solution was selected for further evaluation in the clinical field effectiveness study.

B. Substantial Evidence

Title: ORM-145704: Emesis induction in dogs. A randomized, double-blind, parallel-group, vehicle-controlled, confirmatory clinical field study (Study number V3111003).

Study Dates: October 19, 2015 to December 22, 2015

Study Locations:

Decatur, Illinois
Hickory, North Carolina
Springfield, Missouri
Quakertown, Pennsylvania
Ocala, Florida
Seminole, Florida

Study Design: This was a multicenter, prospective, randomized, masked, vehicle-controlled field study.

Objective: To demonstrate the effectiveness, field safety, and usability of ropinirole ophthalmic solution for induction of emesis in dogs. The study was conducted in accordance with good clinical practice (GCP) guidelines.

Study Animals: There were 132 client-owned dogs enrolled in the study with 100 dogs in the ropinirole group and 32 in the vehicle control group. There were 12 intact females, 12 intact males, 58 spayed females, and 50 neutered males enrolled. The most commonly enrolled breed classification was mixed (30%), Boxer (5.3%), Golden Retriever (5.3%), Labrador Retriever (4.5%), and Shih Tzu (4.5%). Dogs ranged in age from 7 months to 15 years, and weighed 1.9 to 66.3 kg, at the time of screening. Common concurrent medications used during the field study included heartworm preventatives, antiparasitics, antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), and corticosteroids.

Experimental Design:

Treatment Groups: The dogs were randomized into two treatment groups in a 3:1 ratio of ropinirole ophthalmic solution and vehicle control resulting in 100 dogs receiving ropinirole (49 male and 51 female) and 32 dogs receiving vehicle control (13 male and 19 female).

Drug Administration: The owner administered the dose in the veterinary clinic under the supervision of the Investigator. The dogs were fed 60 (± 30) minutes prior to dose administration. The drops were administered into the eyes according to the dosing table (Table II.1) resulting in a target dose of 3.75

mg/m² with a dose range of 2.7 - 5.4 mg/m². A dose of 2 or more drops was divided into both eyes. A dose of 6 or 8 drops was divided into an initial dose of 4 drops (2 drops in each eye) followed 2 minutes later by the remaining number of drops divided into both eyes.

Table II.1: Dose Administration

Body Weight (Kg)	Body Weight (lb)	Number of Eye Drops Ropinirole	Number of Eye Drops Vehicle Control
1.8 - 5	4 - 11.1	1	1
5.1 - 10	11.2 - 22.1	2	2
10.1 - 20	22.2 - 44.1	3	3
20.1 - 35	44.2 - 77.2	4	4
35.1 - 60	77.3 - 132.3	6	6
60.1 - 100	132.4 - 220.5	8	8

If the dog did not vomit within 20 minutes, the dose was repeated. If the duration between the first and last vomiting episodes was greater than 1 hour, the Investigator could administer an antiemetic.

Inclusion criteria: Signed owner consent; dog at least 1.8 kg; and dog was healthy or had mild systemic disease (class I or class II) based on American Society of Anesthesiologists physical status classification.

Exclusion criteria: Dog was pregnant or lactating; had treatment within one week of study onset with dopamine agonists or antagonists or medications with known antiemetic properties including antihistamines and maropitant; had disease for which induction of vomiting would be contraindicated; concurrent participation in any other clinical study; or received administration of any other investigational drug within 14 days of study.

Measurements and Observations: Prior to administration of dose, baseline physical examination (including ocular examination, heart rate, respiratory rate, body weight, and body temperature), hematology, serum chemistry, and urinalysis assessments were performed. These were also assessed again at the end of study visit 3 to 5 days after dose administration.

Dogs were monitored in the veterinary clinic for 8 hours after dosing. After dosing, the time of each vomition and description of the vomit (foam, liquid, solid) were recorded. Ocular tolerance was evaluated pre-dose; at 30 minutes, 2 hours, 4 hours, and 8 hours post dose; and at the end of study visit. The eyes were monitored for conjunctival hyperemia, conjunctival swelling, conjunctival discharge, ocular discomfort (such as rubbing/scratching), protrusion of the third eyelid, and blepharospasm. Ocular findings were assessed on a scale of none, mild, moderate, or severe. Fluorescein stain uptake was measured 8 hours after dose administration and at the end of study visit.

Statistical Methods: The analyses of the effectiveness variables were conducted on the per protocol population, which comprised those dogs without significant protocol violations.

The primary effectiveness variable was treatment success or failure. The dog was classified as a treatment success if it vomited within 30 minutes after the initial administration regardless of whether or not it received a second dose at 20 minutes.

Treatment response in the ropinirole group was analyzed using a generalized linear mixed model, using treatment success or failure as a binomial random variable and assuming a logit link. The model included study site as a random effect. A 95% confidence interval around the estimated success rate was generated, and ropinirole was considered effective if the lower bound of the confidence interval was above 70%. All the study sites that enrolled at least 2 dogs in the ropinirole group were included in the effectiveness analysis.

Results: The ophthalmic solution was successfully administered to all 132 dogs.

Effectiveness was evaluated in 128 dogs (99 dogs in the ropinirole group and 29 dogs in the vehicle group). Four dogs were excluded from the effectiveness analysis. One dog in the ropinirole group was excluded because that was the only dog enrolled at that site; two dogs in the vehicle control group were excluded because of the use of concomitant medications not allowed per protocol; and one dog in the vehicle control group was excluded because the second dose was administered 7 minutes late. Treatment success was defined for each dog as vomiting within 30 minutes of treatment. Ninety-four of the 99 dogs in the ropinirole group vomited within 30 minutes of treatment. One dog in the vehicle group vomited at 46 minutes. The estimated success rate in the ropinirole group was 96.9% and the confidence interval around the estimated success rate is (83.1%, 99.5%). The lower bound is above the predefined minimum of 70%.

Table II.2: Number and Percent Effectiveness for CLEVOR[®] and Vehicle Control

Time to Vomition	CLEVOR[®] (n=99)	Vehicle Control (n=29)
0 - 30 minutes	94 (95%)	0 (0%)

Time to first vomition: Eighty-five dogs in the ropinirole group vomited within 20 minutes and therefore did not require a second dose. The time to first vomition ranged from 3 minutes to 37 minutes with a mean time to vomition of 12 minutes. Fifty dogs vomited within 10 minutes.

The following five dogs were considered treatment failures: two dogs in the ropinirole group received a second dose and vomited 33 and 37 minutes, respectively, after the first dose administration. Three dogs in the ropinirole group did not vomit despite receiving a second dose.

Duration of vomiting: The mean duration between first and last vomiting episode was 23 minutes (range 0 to 108 minutes) with 24 dogs having a vomiting duration longer than 30 minutes and 8 dogs having a vomiting duration longer than 1 hour. Of the 8 dogs with a vomiting duration longer than 1 hour, 5 dogs received an antiemetic at the Investigator's discretion.

Number of vomiting episodes: There was a mean of 4.8 vomiting episodes per dog (range 0 to 13 episodes of vomiting).

Description of vomited material (form, fluid, or solid): The dogs were fed 60 minutes (\pm 30 minutes) prior to induction of vomiting. Of the 94 dogs in the ropinirole group that vomited, 90 dogs vomited the food they were fed prior to administration. The other 4 dogs were noted to vomit fluid or foam with no mention of food.

Physical examination: Tachycardia (elevated heart rates above 160 beats per minute (bpm)) occurred in the ropinirole group but not the control group. Examination 30 minutes after dosing recorded 14 dogs (14%) in the ropinirole group with tachycardia (range 162 - 294 bpm). Examination 2 hours after dosing recorded tachycardia (range 168 - 228 bpm) in 8 dogs. The tachycardia resolved in all but 2 dogs by 4 hours after dose administration. No treatment for the tachycardia was administered. Four dogs in the ropinirole group had pre-existing heart murmurs or were receiving cardiac medications at enrollment. Of these 4 dogs, only one dog developed an elevated heart rate of 162 bpm at 8 hours after dose administration.

Clinical pathology: Two dogs in the ropinirole group with normal liver enzyme values at screening had reported increased serum alanine aminotransferase (ALT) at the end of study visit bloodwork. One dog had increased ALT values from 40 U/L at screening to 207 U/L at end of study (reference range 18 - 121 U/L) and one dog had increased ALT values from 23 U/L at screening to 187 U/L at end of study. Of these two dogs, one also developed an increased serum aspartate aminotransferase (AST) from 35 U/L at screening to 73 U/L at end of study (reference range 16 - 55 U/L).

A third dog in the ropinirole group had elevated serum AST, ALT, and alkaline phosphatase values at screening. The dog's ALT, alkaline phosphatase, and total bilirubin values increased after treatment. The values are listed in Table II.3 below. No apparent cause could be determined for the elevations in liver enzyme values.

Table II.3: Elevated clinical pathology results in one dog administered ropinirole

Variable	Screening	End of Study (EOS)	Three Weeks after EOS	Normal Range
ALT (U/L)	193	1006	351	18 - 121 U/L
AST (U/L)	73	55	16	16 - 55 U/L
Alkaline phosphatase (U/L)	33	509	200	5 - 160 U/L
Total Bilirubin (mg/dL)	0.2	1.2	0.3	0 - 0.3 mg/dL

One dog in the ropinirole group with a normal prothrombin time of 7.6 seconds (range 6.3 - 13.3 seconds) at screening had an increased value at the end of study of 55.5 seconds.

Two dogs in the ropinirole group with normal blood glucose values at screening had decreased blood glucose values (54 and 59 mg/dL respectively, reference range 63 - 114 mg/dL) reported at the end of study.

The ropinirole group had increased incidence of crystalluria (13 dogs) and pyuria (12 dogs) compared to the vehicle control group (3 and 4 dogs, respectively).

Ocular tolerance: Ropinirole administration in the eye resulted in increased signs of blepharospasm, conjunctival discharge, conjunctival hyperemia, conjunctival swelling, and protrusion of the third eyelid. The majority of the signs resolved within 8 hours.

Fluorescein staining: One Shih-Tzu dog in the ropinirole group had normal findings 8 hours after dosing but developed positive fluorescein stain uptake with an associated corneal ulceration recorded at the end of study visit. One Chinese Crested dog in the ropinirole group had faint positive fluorescein stain uptake 8 hours after dosing. This dog required no treatment and had a normal examination at the end of study visit.

Observations: The ropinirole group had increased incidence of salivation, vomiting, quiet demeanor, depression or lethargy, and acting anxious or trembling at the 30-minute timepoint when compared to the vehicle control group. The clinical signs resolved by 8 hours after dose administration.

The following table (Table II.4) shows the number of dogs exhibiting ocular, systemic, and clinical pathology adverse reactions.

Adverse Reactions:

Table II.4: Adverse Reactions Reported During the Study (all dogs)

Organ System	Adverse Reaction	CLEVOR® (N=100)	Vehicle control (N=32)
Ocular	Conjunctival hyperemia ^a	51 (51%)	6 (19%)
	Protrusion of the third eyelid ^a	38 (38%)	1 (3%)
	Conjunctival discharge ^a	30 (30%)	1 (3%)
	Blepharospasm ^a	19 (19%)	0
	Conjunctival swelling ^a	3 (3%)	0
	Scratching/rubbing of eyes ^a	4 (4%)	0
	Corneal ulceration	1 (1%)	0

Organ System	Adverse Reaction	CLEVOR® (N=100)	Vehicle control (N=32)
	Corneal fluorescein uptake without ulceration	1 (1%)	0
Systemic	Lethargy	41 (41%)	0
	Tachycardia (>160 bpm) ^{a,b}	14 (14%)	0
	Vomiting duration longer than one hour	8 (8%)	0
	Salivation	3 (3%)	1 (3%)
	Trembling	3 (3%)	0
	Diarrhea or soft stool	2 (2%)	1 (3%)
	Anxious	1 (1%)	0
	Borborygmi	1 (1%)	0
Clinical Pathology	Crystalluria ^c	13 (20%)	3 (15%)
	Pyuria ^c	12 (18%)	3 (15%)
	Increased liver enzymes ^d	3 (3%)	0
	Decreased blood glucose	2 (2%)	0
	Increased prothrombin time	1 (1%)	0

^a Assessment performed 30 minutes after dose administration

^b Tachycardia resolved for most dogs within 4 hours after dose administration

^c Urinalysis results were reported for only 86 dogs (66 administered CLEVOR® and 20 control)

^d All three dogs had elevated alanine aminotransferase. Additionally, one of the dogs also had an elevated aspartate aminotransferase and another of the dogs also had an elevated alkaline phosphatase and total bilirubin

Note: If any animal experienced the event more than once, only the first occurrence was tabulated.

Conclusion: Treatment with ropinirole ophthalmic solution administered into the eye at 3.75 mg/m² (2.7 - 5.4 mg/m²) was safe and effective for the induction of vomiting in dogs. The most common adverse effects were local ocular irritation related to the route of administration, including conjunctival hyperemia, protrusion of the third eyelid, conjunctival discharge, blepharospasm; and systemic effects related to the dopamine agonist drug class, including lethargy, tachycardia, and prolonged vomiting.

III. TARGET ANIMAL SAFETY

The safety of CLEVOR[®] was demonstrated in one laboratory study described below (III.A. Margin of Safety Study) in which 24 Beagle dogs were dosed with CLEVOR[®] twice daily for 3 days at either 1, 3, or 5X doses. Drug-related effects included local ocular effects related to the route of administration, such as positive fluorescein staining, blepharospasm, conjunctival discharge, ocular hyperemia, conjunctival swelling, ptosis, and protrusion of the third eyelid; and systemic effects such as vomiting, tremors, lethargy, increased heart rates, and decreases in blood pressure. CLEVOR[®] is a dopamine agonist and the systemic drug-related effects are directly related to this class of drug. The systemic drug-related effects resolved within 6 hours after dosing. This study supports the safe use of CLEVOR[®] for the induction of vomiting when administered topically into the eye, at a dose of 3.75 mg/m² (dose band 2.7 - 5.4 mg/m²) administered twice, 20 minutes apart.

Three laboratory studies (See III.B. Studies to Address Protracted Vomiting) were conducted to determine whether metoclopramide (dopamine D2 antagonist), domperidone (dopamine D2 antagonist), or maropitant (neurokinin-1 antagonist) where suitable to stop protracted ropinirole-induced vomiting. The most suitable treatment in the veterinary setting to stop protracted ropinirole-induced vomiting and ameliorate ropinirole-induced clinical signs was determined to be metoclopramide.

A. Margin of Safety Study

Title: Target Animal Safety Study in the Beagle Dog, Study No. ORM-145704 (Sponsor Study No. 508037)

Type of Study: Laboratory study

Study Dates: August 3, 2015 to September 11, 2015

Study Location: WIL Research Europe B.V., The Netherlands

Study Design:

Objective: To evaluate the safety of ropinirole ophthalmic solution in Beagle dogs for 3 days. The study was conducted in accordance with good laboratory practice (GLP) regulations.

Study Animals: Thirty-two Beagle dogs, 4.5 - 5.5 months old, weighing 5.2 - 7.6 kg at the start of treatment. Dogs were acclimatized for 2 weeks prior to study start. Dogs were vaccinated and dewormed prior to study acclimation. Dogs were determined to be healthy based on physical examination and clinical pathology.

Experimental Design: Dogs were randomized to cohort and treatment group (saline: Group 1 or ropinirole: Groups 2 - 4).

Table III.1: Treatment Groups and Dosages

Group No.	Group	No. of eye drops/dog/day ^b	Actual Dose: Body surface area (mg/m ² /day) ^c	Converted Dose: Body weight (mg/kg/day)	No. of dogs
1 ^a	0X	4	0	0	4 males 4 females
2	1X ^d	4	8.5 - 10.6	0.45 - 0.62	4 males 4 females
3	3X	16	35.2 - 40.9	1.88 - 2.36	4 males 4 females
4	5X	24	49.5 - 58.9	2.56 - 3.29	4 males 4 females

^a Physiologic sterile saline (0.9% NaCl), non-ophthalmic solution (pH 5)

^b A drop volume of 27 µL was applied; half the drops were administered in session 1 and half the drops were administered in session 2.

^c Body surface area (BSA) was calculated using $BSA = 10.1 \times (\text{body wt. in kg})^{0.67/100}$.

^d The target 1X dose was as close to 10.8 mg/m²/day as possible, without exceeding that dose. This represents the maximum daily clinical dose in the case where the initial dose needs to be repeated (i.e. two doses 20 minute apart).

Drug Administration: Dogs were dosed in 2 sessions each day, with 20 minutes between the first dose of the first session and the first dose of the second session. Dogs were dosed for 3 consecutive days.

Within 1 session, dogs were dosed once for Groups 1 and 2, twice for Group 3, and 3 times for Group 4. The time between the doses was 2 minutes.

Table III.2: Dosing Sessions- Number of Drops Administered

Group No.	S1 OS	S1 OD	P	S1 OS	S1 OD	P	S1 OS	S1 OD	Wait	S2 OS	S2 OD	P	S2 OS	S2 OD	P	S2 OS	S2 OD
1	1	1	-	-	-	-	-	-	wait	1	1	-	-	-	-	-	-
2	1	1	-	-	-	-	-	-	wait	1	1	-	-	-	-	-	-
3	2	2	P	2	2	-	-	-	wait	2	2	P	2	2	-	-	-
4	2	2	P	2	2	P	2	2	wait	2	2	P	2	2	P	2	2

S1 = session 1, S2 = session 2; OS = left eye, OD = right eye

P= 2 minute pause between dose administration

Wait= 20 minute waiting period between sessions 1 and 2

Measurements and Observations: Observations for mortality and morbidity were conducted twice daily. Clinical observations and examinations, body weight, food consumption, ophthalmic examinations, Schirmer Tear Test (STT), Intraocular Pressure (IOP), fluorescein staining, electrocardiogram, indirect blood pressure,

complete blood count, serum chemistry, urinalysis, necropsy, organ weights, bone marrow smear, and histopathology were evaluated. Euthanasia and necropsy was performed on Day 4.

Statistical Methods: Analysis of variance (ANOVA) was used to analyze all continuous variables measured once during the study. The statistical model included treatment, sex and the treatment-by-sex interaction as fixed effects. For variables measured more than once during the study, a repeated measures analysis of covariance was used, adding the following fixed effects to the ANOVA model: time and the interactions treatment-by-time, sex-by-time and treatment-by-sex-by-time. If multiple pre-treatment values existed, the value nearest to the first day of dosing was included as a covariate. All fixed effects were tested at the 0.10 level of significance. Follow-up mean contrasts between control and each dose group were performed if significant treatment or treatment interaction effects were detected. All mean contrasts were performed at the 0.10 level of significance with no multiplicity adjustment.

Results:

Clinical Observations and Examinations: There were no clinically relevant findings on physical examinations conducted prior to dosing and 6 hours after dosing. After dosing with ropinirole, clinical observations included vomiting (lasting up to 2 hours), retching, hunched posture, labored respiration, salivation, tremors, lethargy, ventral or lateral recumbency, ocular discharge and hyperemia, blepharospasm, ptosis, and conjunctival erythema. Dogs returned to normal within 6 hours post-dosing.

None of the dogs in the saline control group vomited. On Day 1, one dog in the 5X ropinirole group did not vomit, but all other dogs in the ropinirole groups did vomit after dose administration. All dogs in the ropinirole groups vomited on Days 2 and 3. Vomiting generally started within 5 - 10 minutes after dose administration and continued up to 2 hours after administration of the first dose. Vomiting occurred as often as every 1 - 2 minutes and the repeated vomiting episodes lasted 1 - 2 hours. Vomiting occurred less frequently on Day 3 than on Days 1 and 2 for most dogs.

Ophthalmic Examinations: There were no clinically relevant effects on STT, IOP, and ophthalmic examination. One dog in the 3X ropinirole group and one dog in the 5X ropinirole group had positive fluorescein staining, although corresponding lesions were not identified on histopathology. Other abnormal findings noted after ropinirole administration included slight conjunctival discharge, slight to moderate conjunctival swelling, slight to severe blepharospasm, and slight protrusion of the third eyelid.

Electrocardiogram (ECG): In the 1X, 3X, and 5X ropinirole groups there was an initial increase in mean heart rate and corresponding decrease in R-R interval at 1-hour post-dose. These findings were statistically significant ($p < 0.0001$) compared to control. There were no clinically relevant signs during the study that were attributable to the increased heart rate.

Temperature: There was a dose dependent trend for decreased rectal temperature 1 - 6 hours post dose administration in the ropinirole groups. All rectal temperatures remained within normal limits.

Food Consumption: Food consumption was measured daily. There was a dose dependent decrease in mean food consumption. Food consumption was decreased in 1/4 males and 1/4 females in the 1X ropinirole group, in 2/4 males and 3/4 females in the 3X ropinirole group, and in 3/4 males and 4/4 females in the 5X ropinirole group compared to baseline.

There was a statistically significant decrease in food consumption for the 3X and 5X ropinirole groups when compared to the control group ($p=0.0192$ and $p=0.0048$, respectively).

Body Weight: Body weight was measured twice during acclimation and on study Days 1 and 4. Three dogs in the 3X ropinirole group and five dogs in the 5X ropinirole group had weight loss between Days 1 and 4. There was a statistically significant difference dose-by-sex-by-time for body weight between the treatment groups ($p=0.0089$).

Necropsy Examination and Histopathology: There were no drug effects on gross or microscopic pathology.

Conclusions: This study supports the safe use of ropinirole when administered by drops into the eye, at a dose of 3.75 mg/m^2 (dose band $2.7 - 5.4 \text{ mg/m}^2$) administered twice, 20 minutes apart. Local ocular effects related to the route of administration, included positive fluorescein staining, blepharospasm, conjunctival discharge, ocular hyperemia, conjunctival swelling, ptosis, and protrusion of the third eyelid. Systemic effects, related to the dopamine agonist drug class, included vomiting, retching, hunched posture, tremors, erythema of mucous membranes, lethargy and ventral or lateral recumbency, increased heart rate, decreases in blood pressure, decreased food consumption, and decreased body weight.

B. Studies to Address Protracted Vomiting

Three laboratory studies were conducted to determine whether metoclopramide (dopamine D2 antagonist), domperidone (dopamine D2 antagonist), or maropitant (neurokinin-1 antagonist) were suitable to stop protracted CLEVOR[®]-induced vomiting.

One study was a comparison between domperidone and metoclopramide. Both metoclopramide (87.5% when administered intravenously) and domperidone (62.5% when administered as an ophthalmic solution and 100% when administered intravenously) stopped the protracted vomiting and helped ameliorate the clinical signs that occur secondary to CLEVOR[®] administration (lethargy, salivation, retching, muscular tremors, and ocular irritation).

A second study was a comparison between maropitant and metoclopramide. Maropitant stopped the protracted vomiting (100% when administered intravenously and 37.5% when administered subcutaneously) but did not have an effect on clinical signs that occurred secondary to CLEVOR[®] administration, including lethargy, muscular tremors, and ocular irritation. Metoclopramide stopped the protracted vomiting (100% when administered subcutaneously) and helped ameliorate the clinical signs that occur secondary to CLEVOR[®] administration.

A third study was a cardiovascular safety and exposure study that administered metoclopramide subcutaneously to stop CLEVOR[®] associated vomiting. Metoclopramide stopped the protracted vomiting (100% when administered subcutaneously).

From the results of these three laboratory studies, it was determined that metoclopramide is suitable for stopping protracted CLEVOR[®]-induced vomiting and ameliorating the clinical signs that occur secondary to CLEVOR[®] administration.

IV. USER SAFETY

This product should be administered by veterinary personnel.

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

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

In case of accidental eye, oral or skin exposure, flush with water. If wearing contact lenses, eyes should be rinsed first, then remove contact lenses and continue rinsing. Remove contaminated clothing. Ropinirole is a dopamine agonist. Seek medical attention if accidental exposure occurs.

Exposure to this drug may cause adverse reactions such as headache, nausea, vomiting, dizziness, orthostatic hypotension, and sleepiness.

Avoid contact with the product if pregnant, planning to become pregnant or breast-feeding, as exposure has been shown to have adverse effects on embryo-fetal development based on rodent studies.

V. 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 CLEVOR[®], when used according to the label, is safe and effective for induction of vomiting 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 for the safe use of the drug

and to assess the patient for contraindications associated with the induction of vomiting. Furthermore, professional expertise is required to monitor the safe use and respond to adverse reactions.

B. Exclusivity

CLEVOR[®], 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 ingredient 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 Animal Drugs @ FDA database or the Green Book on the FDA website.