Date of Approval: November 2, 2012

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-346

OroCAM

(meloxicam)
Transmucosal Oral Spray
Dogs

For the control of pain and inflammation associated with osteoarthritis in dogs.

Sponsored by:

Abbott Laboratories

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I. GENERAL INFORMATION:

A. File Number:	NADA 141-346
B. Sponsor:	Abbott Laboratories North Chicago, IL 60064 Drug Labeler Code: 000074
C. Proprietary Name:	OroCAM
D. Established Name:	Meloxicam
E. Pharmacological Category:	Non-Steroidal Anti-Inflammatory (NSAID)
F. Dosage Form:	Transmucosal Oral Spray
G. Amount of Active Ingredient:	6 mL vial – pump delivers 0.25 mg/spray 11 mL vial – pump delivers 0.5 mg/spray 33 mL vial – pump delivers 1.075 mg/spray
H. How Supplied:	OroCAM is supplied in three vial sizes containing 6 mL, 11 mL, and 33 mL of meloxicam solution. Each vial has a different metered dose pump delivering a dose of 0.25 mg, 0.5 mg, or 1.075 mg meloxicam, per spray, respectively.
I. How Dispensed:	Rx
J. Dosage:	0.1 mg/kg, once per day
K. Route of Administration:	Oral
L. Species/Class:	Dogs
M. Indication:	For the control of pain and inflammation associated with osteoarthritis in dogs.

II. EFFECTIVENESS:

Dosage Characterization:

A. Comparative Bioavailability Study

1. Title: A Novel Meloxicam Formulation Administered Orally via Transmucosal Oral Spray: A Comparative Bioavailability Study in Dogs

2. Type of Study: Comparative bioavailability study

3. Study Director: Erin Ivey Weich, DVM
   Las Cruces, NM

4. General Design:

   a. Purpose: The objective of this study was to compare the bioavailability of meloxicam transmucosal oral spray (TMOS) to meloxicam oral suspension (METACAM).

   b. Test Animals: Twenty adult female Beagle dogs, weighing between 10.1 and 11.4 kg.

   c. Treatment Groups: The study was an *in vivo* comparative bioavailability study in dogs utilizing meloxicam transmucosal oral spray containing 5 mg meloxicam/mL and the reference product METACAM Oral Suspension containing 1.5 mg meloxicam/mL. The study was designed as a single dose, two treatment, two sequence, two period, cross-over conducted in healthy adult dogs. There was a wash out period of 21 days between treatments. The study groups and treatments/periods are shown in the table below.

Table 1. Treatment Groups for Comparative Bioavailability Study

Treatment Group	Number of Animals	Period 1	Period 2
Group A	10	METACAM Oral Suspension	Meloxicam Oral Spray
Group B	10	Meloxicam Oral Spray	METACAM Oral Suspension

   d. Dosage Form: The test product was meloxicam (5 mg meloxicam/mL) in a suspension of polymer for transmucosal administration (meloxicam transmucosal oral spray). It was and packaged in clear screw-capped glass bottles with a spray applicator.

   e. Route of Administration: Meloxicam transmucosal oral spray was administered as four sprays (representing a 2 mg meloxicam dose) to the buccal surface of the oral cavity (two sprays administered per side). The control article was administered in the oral cavity at a dose volume of 1.3 ml orally to equal the 2 mg meloxicam dose of the transmucosal spray.

   f. Dosage Used: In each period the test and reference products were administered once at a target dose of approximately 0.2 mg meloxicam per

kg of body weight (2 mg meloxicam/animal based on a 10 kg bodyweight dog) 30 minutes after the dog had been fed its morning ration.

g. Treatment Duration: Single administration.

h. Study Evaluations:

Twenty adult female Beagle dogs, weighing between 10.1 and 11.4 kg, were blocked in groups of two by body weight. Dogs were then randomly allocated within blocks to each group and administered either meloxicam transmucosal oral spray or METACAM Oral Suspension alternately in each period.

Personnel responsible for in-life assessments, as well as personnel responsible for dose administration and blood sampling, were not blinded to treatment. Personnel responsible for analysis of the plasma samples were blinded to treatment.

Physical examinations were conducted on study days -14, -1, and 20. Daily observations were performed twice daily by animal care personnel beginning at Day -14 until the end of the study on Day 26. Body weights following overnight fasting were obtained on study days -2, 8, 14, and within 24 hours prior to each dose administration (study days 0 and 20). Dose site irritation observations were conducted at the test product application site prior to dosing and post-dosing at each blood collection time point.

During each period, blood samples for bioanalytical analysis of meloxicam were collected on day -1 before administration, immediately prior to dosing, and at 15 and 30 minutes and 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, and 120 hours after administration. Meloxicam was quantified in plasma by means of a validated LC-MS/MS method.

Pharmacokinetic parameters were calculated for the test and reference products using non-compartmental approach based upon the observed time-plasma meloxicam concentrations from each animal. For C_{max}, AUC_{last}, and AUC_{inf} parameters, data were analyzed statistically by ANOVA.

5. Results:

Each animal was administered 2 mg meloxicam. All animals weighed between 10.2 and 11.4 kilograms on study day -1 and between 10.0 and 11.4 kg on day 20. Therefore, the dose administered to all animals was between 0.18 mg/kg and 0.20 mg/kg.

The results of the study are summarized below:

Table 2. Mean (1SD) Plasma Meloxicam Pharmacokinetics Parameters

Parameter	Meloxicam TMOS	Metacam Oral Suspension
C_{max}, µg/mL	0.6187 (0.0552)	0.6082 (0.0665)
T_{max}, hr	4.5 [0.5, 8]*	6.5 [2, 12]*
C_{last}, µg/mL	0.0407 (0.0149)	0.0428 (0.0125)
Ke, /hr	0.02341 (0.0031)	0.0230 (0.0025)
Half-life, hr	30.053 (3.672)	30.383 (3.060)
AUC_{last}, hr*µg/mL	25.350 (3.695)	25.980 (3.252)
AUC_{inf}, hr*µg/mL	27.190 (4.466)	27.900 (3.848)
CL/F, L/hr/kg	0.0070 (0.0013)	0.0066 (0.0010)
V/F, L/kg	0.3000 (0.0247)	0.2865 (0.0271)

*Range of observed values in brackets [].

ANOVA revealed no statistically significant differences at the 5% level of significance between products for any of the parameters tested (C_{max}, AUC_{inf}, AUC_{last}). Mean C_{max} is 2% greater following administration of the test transmucosal oral spray, but overall mean absorption (AUC) is 98% of the reference METACAM Oral Suspension. The mean T_{max} is 2.0 hours (31%) less for meloxicam TMOS.

At dosing, the following observations were recorded for each treatment. In the METACAM group on day 0 one animal coughed and salivated after dosing, and on day 21 one animal coughed/gagged after dosing. In the meloxicam transmucosal oral spray group, on study day 0 three animals were noted to be licking and chewing, and on study day 21 eight animals were noted to be licking, chewing, or shaking their head after dosing. These observations did not affect dosing. Physical examinations (conducted throughout the study) and dose site irritancy observations (generated prior to dosing and post dosing at each blood collection time) showed no adverse findings.

6. Conclusion:

The results obtained in this comparative bioavailability study support the proposed therapeutic dosage (0.1 mg/kg) of meloxicam transmucosal oral spray (5 mg meloxicam/mL).

B. Pharmacokinetic Study to Demonstrate Transmucosal Absorption

1. Objectives:

   a. To determine if meloxicam is absorbed through the oral mucosa
   b. To estimate, based on previous studies, the extent to which meloxicam is absorbed through the oral mucosa

2. Animals:

   The investigation involved three female Beagle dogs, ages 1-2 years, with body weights of 6-8 kg.

3. Procedure:

   Animals were fasted overnight through approximately 4 hours after full recovery from anesthesia. Animals were premedicated with glycopyrrolate and induced and maintained with isofluorane. The esophagus was obstructed with the inflated cuff of an endotracheal tube. The animal was placed in lateral recumbency and the transmucosal oral spray (TMOS) was administered with the head held such that the dose would not drain out of or towards the back of the mouth.

4. Drug Administration:

   To administer the meloxicam TMOS, the commissure of the dog's lips were grasped and pulled away from the gums opening the buccal space. The mouth was not opened any wider than necessary to facilitate the meloxicam TMOS application. The spray was directed caudally and towards the gingival and/or buccal mucosal surfaces. The pump head was depressed fully, ensuring no spray escaped from the mouth. Each animal was administered a 0.1 mg/kg dose of a 4.66% meloxicam solution via a pump spray. Blood (approximately 3 mL) was collected from each animal pre-dose, and at 5 and 30 minutes and 1, 2, 4, 8, 12, 24 and 72 hours post-dose.

5. Results:

   Absorption of meloxicam through the oral mucosa was demonstrated in all three dogs. In each animal, the maximum concentration (C_{max}) was achieved 2 hours after dosing. A secondary peak or shoulder was seen in all three dogs at 8 hours.

   For comparison, the results from Study VP05-10-C-MX05 (with esophageal occlusion) and Study VP05-10-C-MX06 (no esophageal occlusion) were evaluated. Study VP05-10-C-MX06 utilized the same dose (0.1 mg/kg) and the same formulation, but the meloxicam TMOS was administered to unanesthetized animals without esophageal occlusion. As seen in Table 3, the two methods of dosing resulted in comparable blood concentration versus time profiles. The AUC0-last estimated in study MX05 was 12.3 µg*hr/mL. The $AUC_{0\text{-last}}$ estimated in MX06 was 11.2 µg*hr/mL. Similarly, the C_{max} associated with study MX05 was 0.39 µg/mL (T_{max} = hr 2) while that observed in study

MX06 was 0.45 µg/mL (T_{max} = hr 2). Therefore, the meloxicam blood concentration/time profiles associated with the two conditions of TMOS delivery are indistinguishable.

Table 3. Relative Bioavailability of Meloxicam TMOS* With or Without Esophageal Occlusion

	VP05-11-C-MX05	VP05-11-C-MX06
$AUC_{0\text{-last}}$[a] (µg*hr/mL)	12.3	11.2
C_{max} (µg/mL)	0.39	0.45
T_{max} (hr)	2.0 ± 0.04	2.0± 0.09
$t_{½}$ (hr)	24.7 (21.7-30.4)	25.7 (23.4-29.0)
AUC ratio MX05/X		1.10
C_{max} ratio MX05/X		0.87

Where X = data from the study in that column
* dose normalized to a 0.1 mg/kg dose
[a] where AUC is from time zero to hr 72 for MX05 and from time zero to hr 120 for MX06. In both studies, all samples were above the LOQ at the last sampling time.

6. Conclusion:

   The data obtained in this study demonstrate that meloxicam, when administered via TMOS, is largely absorbed by transmucosal absorption.

Substantial Evidence:

C. Field Effectiveness Study

1. Title: Placebo-Controlled Field Efficacy Trial of Meloxicam Administered Orally Via Transmucosal Oral Spray, in Client-Owned Dogs with Osteoarthritis

2. Type of Study: Field Study

3. Study dates: April 25, 2010 - November 26, 2010

4. Investigators:

Dr. Samuel Geller	Quakertown, PA
Dr. Dave Lukof	Harleysville, PA
Dr. Victor Manoharan	West Palm Beach, FL
Dr. Jay Alan Butan	North Lake Worth, FL
Dr. Terry Clekis	Bradenton, FL
Dr. Stuart Gluckman	Mendon, NY
Dr. Susan Hubbard	Rochester NY
Dr. Roger Sifferman	Springfield, MO
Dr. Dean Rund	Springfield, MO
Dr. Melissa Wiest	O'Fallon, MO
Dr. Gary Brotze	New Braunfels, TX
Dr. Peter Davis	Augusta, ME
Dr. Roberta Jackson	Dover, DE
Dr. Howard T. Robinson	Fort Collins, CO

5. Study Design:

   a. Objective: The study was designed to evaluate the safety and effectiveness of meloxicam administered via transmucosal oral spray for the control of pain and inflammation associated with canine osteoarthritis. In addition, the study was designed to evaluate the transmucosal oral spray dose procedure.

   b. Study Animals: Two hundred eighty client-owned dogs participated in the study. The dogs ranged in age from 1.3-17.7 years and in weight from 2.5-56.3 kg.

   c. Treatment groups: The animals were randomized into two treatment groups in a 2:1 ratio of meloxicam transmucosal oral spray and vehicle control (placebo), respectively. See the following table.

Table 4. Treatment Groups

Treatment Group	Meloxicam Dose
Treated	0.1 mg/kg, once per day
Placebo	0 mg/kg, once per day

   d. Drug Administration: A dose of 0.1 mg/kg was administered using the appropriate number of sprays based on the animal's body weight. See Dosing Table below. Treatment was administered once daily for a total of 28 days. The treated group received meloxicam solution (5 mg meloxicam/mL) in a suspension of polymer for transmucosal administration. The control group received placebo oral spray (vehicle). Test article and placebo were packaged in 6, 11, or 33 mL clear glass screw-capped bottles with accompanying spray pumps. The size of the pump was specific to each of the bottle sizes to deliver the appropriate volume of test material.

Table 5. Dosing Table

Weight Range (kg)	No. of Sprays/ Treatment	Pump **Size (µL)**	Dose Volume **(µL)**	Dose Amount (mg)*	Dosage Range (mg/kg)*
2.1 - 3.7	1	50	50	0.25	0.07 – 0.12
3.8 - 6.2	2	50	100	0.50	0.08 – 0.13
6.3 – 8.3	3	50	150	0.75	0.09 – 0.12
8.4 – 12.5	2	100	200	1.00	0.08 - 0.12
12.6 – 18.8	3	100	300	1.50	0.08 - 0.12
18.9 – 27.1	2	215	430	2.15	0.08 – 0.11
27.2 – 40.5	3	215	645	3.23	0.08 – 0.12
40.6 – 54.0	4	215	860	4.30	0.08 – 0.11
54.1 – 57.2	5	215	1075	5.38	0.09 – 0.10

*Dogs in the placebo group received an equivalent volume but 0 mg (0 mg/kg) meloxicam.

e. Inclusion Criteria:
   1) Study candidates were required to be at least 6 months old, of any sex or breed, weighing 2.1-57.2 kg.
   2) Dogs had to be generally healthy with no evidence of severe systemic disease.
   3) Dogs had to demonstrate clinical signs of osteoarthritis that required medication (all five criteria must have been met):
      (a) Lameness/impaired activity(s)
      (b) Pain during palpation of an affected joint
      (c) Radiographic evidence of osteoarthritis involving a joint that is painful. Eligible joints included: shoulder, elbow, carpal, hip, knee, or tarsal joint
      (d) Combined lameness and pain score (see Tables 6 and 7 below) of ≥ 5 at Enrollment
      (e) Client Specific Outcome Measure (CSOM) of ≥ 8 at the Enrollment visit (See description below).
   4) Cases in which lameness was due to causes other than osteoarthritis were excluded.

Table 6. Lameness Score

Score	Descriptor
1	Stands and ambulates normally
2	Mild offloading (redistribution of body weight off affected limb) OR mild lameness while ambulating
3	Moderate offloading OR moderate lameness while ambulating
4	Severe offloading OR severe lameness while ambulating
5	Three-legged stance OR three-legged gait

Table 7. Pain Score

Score	Descriptor
1	No response detectable to palpation and manipulation of the limb
2	Mild response to palpation and manipulation such as turns head toward limb
3	Moderate response to palpation and manipulation such as withdraws limb
4	Severe pain response to palpation and manipulation such as withdraws limb upon minimal movement of joint, vocalizes or becomes aggressive
5	Does not allow palpation or manipulation

Client Specific Outcome Measures (CSOM):
The degree of impairment recognized by the owner was measured using a CSOM system in which the owner identified three activities that were impaired compared to when the dog was considered normal. Owners were asked to be very specific and to indicate both the places and the times when activities were impaired. During the Enrollment visit, owners were asked to rate the degree of impairment associated with these very specific activities. A five-point scale was used:

1=no problem
2=mildly problematic
3=moderately problematic
4=severely problematic
5=impossible.

f. Measurements and Observations:

Safety and effectiveness were evaluated throughout the study with a series of telephone contacts and visits to the study sites on Days 7, 14, 28, and 42.

Day 7:
Owners were contacted by telephone to assess patient status.

Day 14:
Owners were contacted by telephone to provide ratings on the five-point scale for CSOM activities. If the CSOM score increased as compared to the CSOM score at the Enrollment visit, the dog was to be discontinued from the study (rescued). If the CSOM score did not change compared to the CSOM score at the Enrollment visit, the owner had the option to rescue the dog from the study or to continue the dog in the study.

Day 28:
The dog returned to the Study Site and the following evaluations were performed:

- a physical examination
- hematology and clinical chemistry evaluation
- owner provided rating of CSOM activities
- veterinary assessment of clinical signs of osteoarthritis.

Two secondary variables were also assessed on Day 28:

- The Owner Global Assessment: owners rated the control of osteoarthritis signs during the trial as "Excellent", "Good", "Fair" or "Poor".
- Each CSOM activity was rated by the owner as "Improved" or "Not Improved".

Day 42:
If no physical exam or laboratory abnormalities were found at the Day 28 visit, only a follow-up phone contact was done to assess for adverse events that may have occurred after Day 28.

If physical exam or laboratory abnormalities were found at Day 28, a visit to the study site was completed. The Day 42 visit included an assessment of adverse events as well as physical examination and laboratory evaluation.

Owners documented their dog's reaction to dosing on a daily basis. The dog's reaction was rated using the following scale:

a= administration of the medication was accomplished with minimal effort or struggling in a short period of time.
b= administration of the medication was accomplished with some effort or struggling in a short period of time.

c= administration of the medication was accomplished with much effort or struggling over a prolonged period of time.

Additionally, on Day 28 owners were asked to indicate whether or not the dose procedure was acceptable.

g. Statistical Methods:

The experimental unit was the individual dog. All animals were included in the safety analysis. Only animals from sites with at least two placebo and two meloxicam cases were included in the statistical analysis for effectiveness. A case that was rescued was considered a treatment failure for all effectiveness assessments. Also, animals with missing Day 28 evaluations due to potentially test article related adverse reactions or due to dose inacceptance were considered treatment failures for all effectiveness assessments.

Effectiveness Variable:
Reduction of at least 2 in total CSOM score at Day 28 compared to CSOM score at the enrollment visit was defined as a treatment success. A decrease of less than 2, no change, or an increase in total score was defined as a treatment failure. Dogs that experienced an increase in any individual CSOM were considered a treatment failure regardless of total CSOM score.

Incidence of treatment success at Day 28 was analyzed for treatment effect using a mixed model logistic regression analysis, assuming a binomial distribution, a logit link and the Kenward-Roger adjustment for degrees of freedom. Treatment was included in the model as a fixed effect. Site and the treatment by site interactions were evaluated as random effects. Treatment effects were tested using a two-side test at the 0.05 level of significance.

Secondary Variables:
The following secondary variables were assessed: total CSOM score at Days 14 and 28, treatment success based on CSOM improvement, improvement based on veterinary efficacy assessment scores (lameness and pain), and treatment success based on owner global assessment.

At Days 14 and 28, total CSOM score was analyzed using a mixed model analysis of covariance with baseline CSOM score as the covariate. Treatment, day, and the treatment-by-day interaction were included in the model as main effects; site and the treatment-by-site interaction were included as random effects.

The remaining secondary effectiveness variables were evaluated for success on Day 28: treatment success based on CSOM improvement, pain, lameness, and treatment success based on owner global assessment. Incidence of treatment success was analyzed for treatment effect using a mixed model logistic regression analysis (GLIMMIX with binomial distribution, logit link, and Kenward-Roger degrees of freedom) with site and treatment-by-site as random effects. Models included treatment as the main effect and random effects site and treatment-by-site interaction.

6. Results:

Effectiveness was evaluated in 258 dogs and field safety was evaluated in 280 dogs. Based on owner evaluated CSOM scores on Day 0 and 28, animals in the meloxicam treated group had a significantly different (p = 0.0030) and numerically higher treatment success compared to animals in the placebo group, with 72.62% versus 46.85% success rates, respectively (back-transformed from the logistic regression).

Table 8. Summary of the Statistical Analysis of the Primary Effectiveness Outcome

Treatment Group	N	Number of Treatment Successes	% **Success†**	SEM[a]	P-value of Treatment Effect
Meloxicam	170	123	72.62%	4.11	0.0030
Placebo	88	42	46.85%	6.08	

†Percent success values were back-transformed from the logistic regression.
[a]SEM Standard Error of the Mean

For the secondary variables, the analysis showed that the treatment-by-day interaction was statistically significant for Total CSOM score (p=0.0452). On both Day 14 and 28, the treatment means were significantly different ($p<0.05$) and numerically lower in the treated group than in the placebo group. The treatment effect was significant for treatment success based on CSOM improvement (p=0.0033) and treatment success based on owner global assessment (p=0.0134). Both showed improvement in the meloxicam-treated group. The treatment effect was not significant for pain or lameness evaluations.

No treatment-related differences were observed in the physical examination findings. Hematology and clinical chemistry analysis suggested a treatment-related decrease in percent neutrophils. Absolute neutrophil counts were not significantly affected.

Dose Acceptance:
The same pump apparatus was used in both treatment groups. There was no apparent change in the level of acceptance over the course of the 28-day treatment period. At the end of the treatment period, owners were asked to indicate whether or not the dose procedure was acceptable. Of the 205 owners that provided a response, 85.1% indicated that the dosing procedure was acceptable, while 14.9% indicated that the dosing procedure was not acceptable.

Owner observations of the dog's reactions to dosing included [reaction (number of dogs exhibiting reaction)]: coughing/gagging (3), sneezing (2), drooling (1), spitting (1), wheezing (1), smacking lips (1), and rubbing face on bedding (1).

7. Adverse Reactions:

There were a total of 79 adverse reactions observed in the meloxicam group (N=187) and 37 adverse reactions observed in the placebo group (N=93); some dogs may have experienced more than one type or occurrence of an adverse reaction. The most common adverse reactions involved the

gastrointestinal system (see Table 9). Non-gastrointestinal adverse reactions were rare and included increased liver enzymes, hematuria, lethargy, polydipsia, and dehydration.

The incidence of adverse reactions observed in the study is tabulated below. The pattern suggests some gastrointestinal effects (vomiting, diarrhea) associated with the test article. The clinical signs were generally mild, transient (lasted 1-4 days during the 28-day study period), and resulted in complete recovery. There were no clinical signs related to increased liver enzymes.

Table 9. Adverse Reactions Reported in the Field Study

Adverse Reaction*	Meloxicam Transmucosal Oral Spray N = 187	Placebo (Vehicle) N = 93
Vomiting	22	6
Increased Liver Enzymes (ALT and/or Alk Phos)	11	6
Diarrhea	8	2
Lethargy	6	2
Inappetence	4	2
Hematuria	1	0
Polydipsia	1	1
Dehydration	1	0

*Dogs may have experienced more than one type or occurrence of an event during the study.

8. Conclusions:

   The clinical study demonstrated that daily administration of meloxicam TMOS at a dose of 0.1 mg/kg for 28 days was effective in controlling the clinical signs of osteoarthritis in dogs.

III. TARGET ANIMAL SAFETY:

A. Margin of Safety Study

1. Title: Target Animal Safety Study of Meloxicam (VEL-504) Administered Orally Via Transmucosal Oral Spray for Six Months in Dogs

2. Type of Study: Six-month laboratory safety study

3. Study Director: Dr. Jonathan Hare
   Stouffville, Ontario, Canada

4. General Design:

   a. Purpose: To determine the safety of meloxicam administered orally via transmucosal oral spay at 1, 2, 3, and 5X the proposed therapeutic dose for 6 months (188 days) in the dog.

b. Test Animals: Twenty male and twenty female Beagle dogs were selected and randomly allocated to five treatment groups of eight dogs each (4 males and 4 females). At study initiation, the age range of the study dogs was between 291 days (9.7 months) and 484 days (16 months). The dogs weighed between 6.6 kg (14.5 lb) and 13.2 kg (29.0 lb).

c. Dosage Form:
   1) Test Article: Meloxicam – liquid solution of meloxicam (5 mg/mL) in a suspension of polymer for transmucosal administration; packaged in clear screw-capped glass bottles with a spray pump that delivers 100 µL per depression.

   2) Control Article: water – packaged the same as the test article.

d. Route of Administration:

   The spray was administered to the oral mucosa. The pump was screwed on to the bottle and primed by depressing it at least 5 times prior to the first use. The pump was primed into a container with absorbent material that was discarded. To administer the test article and control products, the commissure of the dog's lips was gently pulled away from the gums. The spray was directed caudally and towards the gingival and/or buccal mucosal surfaces. The pump was depressed fully, ensuring no spray escaped from the mouth. On day 169/167 of the study an amendment was implemented to address pump failures. If the pump did not fully actuate, the pump was shaken, re-primed, replaced in the dog's mouth, and the pump re-actuated. In these cases, the dog received an additional full pump in addition to the partially actuated pump.

e. Dosages Used:

Table 10. Control and Treatment Groups

Treatment Group	Dose	Number and Sex of Animals
T0 (control)	0x (water, volume equivalent to 5x)	4M, 4F
T1	1x, 0.12 mg/kg (0.12 – 0.18 mg/kg)*	4M, 4F
T2	2x, 0.24 mg/kg (0.24 – 0.31 mg/kg)*	4M, 4F
T3	3x, 0.36 mg/kg (0.36 – 0.43 mg/kg)*	4M, 4F
T5	5x, 0.60 mg/kg (0.60 – 0.67 mg/kg)*	4M, 4F

*Actual dose range administered to study dogs.

f. Variables Measured:
Clinical Observations, physical examinations, body weight, food consumption, dose site observations, buccal mucosal bleeding time, CBC, serum biochemistry, urinalysis, endoscopy of the stomach and duodenum, meloxicam concentration in the blood, ophthalmologic examination, and gross and histopathologic examination.

g. Statistical Analysis:
All continuous data were analyzed using mixed models including treatment, gender, and the treatment-by-gender interaction as fixed effects. The model for continuous variables measured over time also included time and all two-way and three-way interactions of the main effects as fixed effects. All repeatedly measured continuous variables except physical examination variables were analyzed using analysis of covariance. Variables measured once were analyzed using analysis of variance.

Endoscopic grade data was analyzed using Wilcoxon's rank sum test.

5. Results:

All dogs survived to termination of the study.

a. Adverse Clinical Effects:
Vomiting, abnormal fecal consistency, and the presence of blood in the fecal material were the main adverse clinical signs observed during the study. There were a higher number of vomiting episodes in the 1x, 2x, 3x, and 5x treatment groups compared to the 0x (control) group. The highest number of vomiting episodes occurred in the 5x treatment group. Episodes of blood in feces were seen in all treatment groups; however, the largest number of dogs exhibiting at least one episode occurred in the 5x group. There were a

similar number of episodes of feces with abnormal consistency in all five groups.

b. Hematology and Clinical Chemistry Evaluations:
White blood cell (WBC) counts decreased below the reference range in two 1x dogs, three 2x dogs, and four 3x dogs. Absolute neutrophil counts decreased below the reference range in one 1x dog, two 2x dogs, and two 3x dogs. One dog in the control group (0x) showed decreased WBC and absolute neutrophil values at all time points, including baseline. All dogs in the 5x group had normal WBC and neutrophil values, except one dog that showed increased individual values above the normal reference range.

Dogs in the 1x, 3x, and 5x treatment groups had statistically significantly different ($P<0.10$) mean albumin values on week 4, as compared to the control (0x) group, with lower values observed in the treated groups. On week 12, mean albumin values remained lower ($P<0.10$) in the 5x treatment group, as compared to the control (0x) group. On week 4, one 1x dog, one 3x dog, and two 5x dogs had individual albumin values below the reference range. One of the 5x dogs showed consistently decreased albumin values through week 26.

Elevated alkaline phosphatase (ALP) values, above the reference range, were seen in four study dogs; one control (0x) dog, one 1x dog, and two 3x dogs. All increases were less than two times the upper limit of the reference range. No individual dogs in the 5x treatment group exhibited elevated ALP values. One 1x dog exhibited an alanine aminotransferase (ALT) value on week 4 that was between two and three times the upper limit of the reference range. This same dog had a mildly elevated ALT value at baseline.

c. Endoscopy:
A flexible endoscope was used to examine the stomach (cardia, fundus, lesser curvature, and pyloric antrum) and the proximal duodenum of each dog. Mucosal lesions noted in each region of the stomach and in the small intestine were graded from 0 to 6. Interpretation of the endoscopy results was difficult, as multiple dogs in the control and treatment groups demonstrated a score of '4' in the pyloric antrum, at baseline and frequently throughout the study period. A score of '4' was defined as (a) greater than 25 punctate erosions or hemorrhage, or (b) 1 to 5 invasive erosions or any striations. Endoscopic lesions in study dogs may have been due to exposure to the investigational drug product, external stressors, or artifact.

In the remaining anatomical regions evaluated, lesions were rare. In the proximal duodenum, one dog in the 1x group, one dog in the 2x group, and one dog in the 3x group exhibited a grade '4' lesion on week 8. Only one dog in the 5x group demonstrated a lesion with a score greater than '1', and this lesion was likely due to artifact from the endoscope itself. One dog in the 2x group exhibited a grade '4' lesion in the fundus on week 26. One dog in the 3x group exhibited a grade '2' lesion (6 to 15 punctate erosions or hemorrhage) in the cardia on week 26. None of the endoscopic lesions correlated with findings on gross pathology examination.

One control (0x) dog had lesion scores of '4' or '5' (greater than 5 invasive erosions) in all regions evaluated on either week 8 or week 26. This dog was diagnosed on week 8 with acute necrotizing enteritis. This dog had measurable meloxicam concentrations detected in plasma samples during the study.

d. Pathology Findings:
Gross examination was performed on all study dogs. Histopathology was originally only performed on all gross abnormalities and on tissues from the 0x (T0) and 5x (T5) treatment groups. Due to the presence of possible treatment-related lesions, histopathology examination was later performed on small intestine specimens from 3x dogs, and stomach specimens from all 1x, 2x, and 3x dogs.

Potential test article-related changes were observed in the gastrointestinal tract of two dogs. One 3x dog was identified as having an ulcer in the fundic mucosa on gross examination. On histopathology, the mucosa was noted to be thin and attenuated with irregular thickness; however, no erosions or ulcers were observed in the section. One 5x dog was noted to have several shallow pink erosions in the duodenal mucosa. On histopathology, villus atrophy was noted with marked dilation of the submucosal glands in the duodenal mucosa. The overlying mucosa showed atrophy of the villi and hyperplasia of the epithelial cells in the crypts.

e. Pharmacokinetics:
   1) Meloxicam Concentrations in Control Dogs:
   Quantifiable meloxicam concentrations were found in all control (0x) dogs, throughout the study. Concentrations were well below the amounts found in dogs in the 1x to 5x treatment groups. Contamination of control dogs with test article was most likely due to the complicated serial dosing schedule during the study. Control group dogs may have received the test article through contact with the hands and clothing of the personnel administering the test article, through contact with study dogs in adjacent pens, or through aerosol contamination. The largest amounts were measured in two dogs, one of which had concentrations on study day 168 that were approximately 10 to 25% of concentrations in the 1x group. A second dog had concentrations on study days 93 and 170 that were approximately 5 to 10% of concentrations in the 1x group. This study dog exhibited frequent episodes of bloody diarrhea throughout the study period. This study dog also showed elevations in ALP on weeks 20 and 26. On week 8, biopsy samples of stomach and small intestine were taken from this dog during a scheduled endoscopy, and acute necrotizing enteritis was diagnosed. No obvious cause was determined, and no treatment was administered. This dog was described as thin, but otherwise healthy, and survived until the end of the study.

   2) Overall Plasma Meloxicam Concentrations: Evaluation of trough meloxicam plasma concentrations indicated that steady state concentrations were achieved during the study. Steady-state plasma meloxicam concentrations increased with dose; the increase was less

than expected. At the 3x dose level, plasma meloxicam concentrations were an average of 2.1 times greater than the concentrations at the 1x dose level. Similarly, concentrations at the 5x dose level were 3.1 times greater than concentrations at the 1x dose level.

3) Pump Failures: There were 77 pump failures noted during the study: T0 (2 failures), T1 (3), T2 (19), T3 (37), and T5 (16). There was not enough evidence to indicate that pump failure/clogging or product settling affected plasma concentrations.

6. Conclusions:

All dogs survived to the end of the 6 month study. Typical NSAID-induced gastrointestinal adverse effects were observed. An adequate safety margin was demonstrated in this study to support the use of meloxicam transmucosal oral spray for the control of pain and inflammation associated with osteoarthritis in dogs.

B. Local Tolerance Study

1. Title: Target Animal Safety and Local Tolerance Study of a Novel Meloxicam Formulation Administered Orally Via Trans Mucosal Oral Spray for Three Months in Dogs

2. Type of Study: 3 month laboratory safety study

3. Study Director: Amanda Walker, BSc
Edinburgh, UK

4. General Design:

a. Test Animals: 16 Beagle dogs; Age range 6-7 months old; Weight range 8.4 – 11.5 kg

b. Dosage Form: Final formulation

c. Dosages Used:

Table 11. Control and Treatment Groups

Test Substance	Daily Dosage	Route	No. Male	No. Female
Group 1 (water)	0 mg/kg (0x)	Spray administered to oral mucosa	8	8
Group 2 (meloxicam, 5 mg/mL solution)	0.2 mg/kg initially on day 0, 0.1 mg/kg (1x) thereafter	Spray administered to oral mucosa	8	8

d. Variables Measured: Clinical observations, dose site observations, urinalyses, fecal analyses, CBC, serum chemistry, and coagulation.

5. Results:

a. Clinical Observations: Three dogs vomited (2 treated dogs, 1 control); four animals had loose feces on several occasions (all control).
b. Dose Site Observations: No treatment-related lesions noted.
c. Clinical Pathology: There were no clinically relevant treatment-related effects.

6. Conclusions:

No treatment-related effects were observed at dose sites. Gastrointestinal effects may be treatment-related.

IV. HUMAN FOOD SAFETY:

This drug is intended for use in dogs, which are non-food animals. 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 OroCAM:

Not for use in humans. Keep this and all medications out of reach of children. Consult a physician in case of accidental ingestion by humans or contact with mucous membranes. Direct contact with skin, eyes, and mucous membranes should be avoided. If contact occurs with skin, the area should be washed immediately with soap and water for at least 20 seconds. In case of contact with eyes, flush immediately with water. Women in late pregnancy should avoid contact with this product.

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 and 21 CFR part 514. The data demonstrate that OroCAM, when used according to the label, is safe and effective for the control of pain and inflammation associated with osteoarthritis 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 properly diagnose osteoarthritis and prescribe appropriate treatment.

B. Exclusivity:

Under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of approval.

C. Patent Information:

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