Approval Date: April 15, 2003

FREEDOM OF INFORMATION SUMMARY

NEW ANIMAL DRUG APPLICATION

NADA 141-213

Metacam® (meloxicam) 0.5 mg/mL and 1.5 mg/mL Oral Suspension

".....indicated for the control of pain and inflammation associated with osteoarthritis in dogs."

Sponsored by:

Boehringer Ingelheim Vetmedica, Inc.
2621 North Belt Highway
St. Joseph, Missouri 64506-2002

FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION:

a.	File Number:	NADA 141-213
b.	Sponsor:	Boehringer Ingelheim Vetmedica, Inc. 2621 North Belt Highway St. Joseph, Missouri 64506 Drug Labeller Code: 000010
c.	Established Name:	meloxicam
d.	Proprietary Name:	Metacam® Oral Suspension
e.	Dosage Form:	Meloxicam is an oral suspension.
f.	How Supplied:	0.5 mg/mL: 15 and 30 mL bottles 1.5 mg/mL: 10, 32 and 100 mL bottles
g.	How Dispensed:	Rx
h.	Amount of Active Ingredients:	0.5 and 1.5 mg/mL
i.	Route of Administration:	This product is designed to be administered orally either mixed with food or placed directly into the mouth.
j.	Species/Class:	Canine/dogs
k.	Recommended Dosage:	Metacam® Oral Suspension should be administered initially at 0.2 mg/kg body weight only on the first day of treatment. For treatments after the first day, Metacam® Oral Suspension should be administered once daily at 0.1 mg/kg body weight.
all		
l.	Pharmacological Category:	non-steroidal anti-inflammatory (NSAID)
m.	Indications:	Metacam® Oral Suspension is indicated for the control of pain and inflammation associated with osteoarthritis in dogs.

2. EFFECTIVENESS:

a. Dosage Characterization:

The results of two pilot studies support the use of an initial oral dose of 0.2 mg/kg followed by the oral daily maintenance dose of 0.1 mg/kg of meloxicam for the control of pain and inflammation associated with osteoarthritis (OA) in dogs.

The first study demonstrated the analgesic and anti-inflammatory properties of meloxicam in a model of acute synovitis by intravenous administration. This masked, randomized, cross-over design used 12 adult dogs to evaluate two dosages of meloxicam and a placebo, using an acute model of intra-articular inflammation. Meloxicam was administered intravenously as a single dose of either 0.1 or 0.5 mg/kg. Following meloxicam or placebo administrations, sodium urate was injected intrasynovially into the femoropatellar joint. In this study, subjective clinical indicators of lameness, force plate gait analysis, and synovial fluid analysis were measures of effectiveness. Meloxicam reduced the subjective clinical indicators of lameness. Based on force plate analysis, meloxicam allowed for a greater force transfer to the affected limb. The study showed that both 0.1 and 0.5 mg/kg meloxicam were effective in reducing signs of acute synovitis by intravenous administration.

The second study was a multiple site field study. The results demonstrated that an initial dose of meloxicam at 0.2 mg/kg followed by a daily maintenance dose of 0.1 mg/kg, was clinically effective. The initial dose of meloxicam was administered subcutaneously or orally in this study in three treatment groups:

Group A - 0.2 mg/kg body weight (b.w.) once daily for 7 days (10 OA dogs),
Group B - a single oral dose of meloxicam (0.2 mg/kg b.w.) followed by 6 days of oral dosing at 0.1 mg/kg b.w. (14 OA dogs), and
Group C - 0.2 mg/kg b.w. meloxicam administered by subcutaneous injection followed by 6 days of oral dosing at 0.1 mg/kg b.w. (11 OA dogs)

A positive response was observed in all three treatment groups based on subjective evaluations of mobility, local inflammation and palpatory pain. One dog in Group A showed an incident of transient gastrointestinal adverse reactions; no gastrointestinal side effects were observed in the other two treatment groups (Groups B or C).

b. Substantial Evidence:

Studies were conducted in dogs to demonstrate the effectiveness of meloxicam in dogs for the control of pain and inflammation associated with osteoarthritis (OA). These field studies were conducted in various locations. Results of these studies demonstrate that meloxicam is effective when administered at an initial dose of 0.2 mg/kg body weight followed by 0.1 mg/kg body weight.

(1) Field Study #1 (635-0180-98-006):

Title: A Field Study Evaluating Meloxicam in Clinical Practice for the Management of Pain and Inflammation Associated with Canine Osteoarthritis

(a) Type of Study: Field study

(b) Investigators:

Name	Clinic	City	State	Zip
Dr. Wallace Diehl	Timberlyne Animal Clinic	Chapel Hill	NC	27514
Dr. Barbara Teter	The Pet Clinic	Omaha	NE	68144
Dr. David Knaak	Limestone Companion Animal Hospital	Bartonville	IL	61607
Dr. Robert Wilbanks	Castle Hills Companion Animal Hospital	San Antonio	TX	78231
Dr. Dean Vicksman	Evans East Animal Hospital	Denver	CO	80222
Dr. Lori Teller	Meyerland Animal Clinic	Houston	TX	77035
Dr. Valerie Kastens	University Pet Clinic	Salt Lake City	UT	84105
Dr. LD Eckermann	Westbury Animal Hospital	Houston	TX	77035
Dr. Timothy Munjar	Surgical Specialty Clinic for Animals	Beaverton	OR	97005
Dr. Kimberly Collett	The Animal Center	Alliance	NE	69301
Dr. Kevin Taylor	Big Hollow Companion Animal Hospital	Peoria	IL	61615
Dr. William H. Craig	Ingram Park Animal Hospital	San Antonio	TX	78238
Dr. Christopher Rodi	Mission Animal & Bird Hospital	Oceanside	CA	92054
Dr. Thomas Liebl	Clinton Parkway Animal Hospital	Lawrence	KS	66047
Dr. Barry Burtis	Bay Cities Animal Hospital	Burlington	Canada	L7R1K3
Dr. Peter Grinberg	Manitou Animal Hospital	Kitchener	Canada	N2C2J6
Dr. Joy Courey	Animal Care Clinic	Brampton	Canada	L6V1A1
Dr. Amanda Glew	Hudson Veterinary Hospital	Hudson	Canada	J0P 1H0
Dr. Erin Robinson	Four Rivers Veterinary Clinic	Ontario	Canada	97914
Dr. Jerry Rayburn	Carter Animal Hospital	Winter Haven	FL	33881
Dr. Gerald Ramsdell	North East Animal Hospital	North East	PA	16428

(c) General Design

1 Purpose: The objectives of this study were: 1) clinically evaluate the safety and effectiveness of meloxicam for the control of pain and inflammation associated with canine osteoarthritis, 2) evaluate the acceptance/palatability of Metacam® Oral Suspension in dogs.

2 Test Animals: Two hundred twenty-four client owned dogs participated in the study. Of the 224 cases, 109 received meloxicam and 115 received a placebo. The dogs ranged in age from 11 months to 14 years of age and ranged in weight from 8 to 169 pounds.

3 Controls: Placebo (similar to meloxicam suspension, except meloxicam active ingredient was omitted).

4 Diagnosis: Dogs with a unilateral or bilateral lameness were eligible for enrollment. The diagnosis of osteoarthritis was based upon demonstration of at least two of the following clinical signs: a) Pain on palpation of affected joint, b) Unwillingness to use affected joint, c) Swelling of affected joint, d) Perceptible heat over affected joint, e) Crepitus of affected joint, or f) Stiffness of affected joint when rising. Radiographic evidence of osteoarthritis must also have been present; 1 = Radiographic evidence of instability (swollen joint, thickened capsule; no degenerative change), 2 = Mild degenerative change (occasional osteophytes), 3 = Moderate degenerative change (osteophytes, subchondral sclerosis) or 4 = Severe degenerative change (osteophytes, subchondral sclerosis, remodeling of bone).

5 Dosage Form: meloxicam injectable solution (5 mg/mL) and Metacam® Oral Suspension (0.5 and 1.5 mg/mL).

6 Route of Administration: Subcutaneous and Oral.

7 Dosages Used: Initial subcutaneous dose at 0.2 mg/kg on day one, followed by 0.1 mg/kg orally once daily.

8 Treatment Duration: The treatment was administered once daily for a total of 14 days.

9 Parameters Measured: The dogs were examined on day 1 (enrollment), day 8 (interim) and day 15 (final). The primary parameters consisted of three components: lameness, weight bearing, and pain upon palpation. The range for each of the three components was 1 to 5, with one being normal.

Lameness:

The dog was observed both standing and walking. An assessment of both the lame leg and the contralateral limb was made using the following scoring system:

1 = stands and walks normally
2 = stands normally with slight lameness when walking
3 = stands normally with obvious lameness when walking
4 = abnormal stance with slight lameness when walking
5 = abnormal stance with obvious lameness when walking

Weight Bearing:

The dog was observed both standing and walking. An assessment of both the lame leg and the contralateral limb was made using the following scoring system:

1 = normal weight bearing on all limbs at rest and when walking
2 = normal weight bearing at rest. Partial weight bearing when walking
3 = partial weight bearing at rest and when walking
4 = partial weight bearing at rest and non-weight bearing when walking

5 = non-weight bearing at rest and when walking

Pain on Palpation:

The investigator palpated and manipulated the affected area and scored the dog's response according to the following list of responses. An assessment of both the lame leg and the contralateral limb were made:

1 = no response detectable to manipulation of the limb
2 = mild response to manipulation, turns head toward limb
3 = moderate response to manipulation, withdraws limb
4 = severe pain response to manipulation, vocalizes or becomes aggressive

At the 8 and 15 day rechecks, the Investigators and Owners each evaluated the dog's overall condition. Investigators categorized each dog's clinical condition as Excellent, Good, Fair, or Poor Improvement. Owners categorized their dog's overall condition as Greatly, Moderately, Slightly, or Not Improved. The Owners also evaluated their dog's ability to rise, mobility, and lameness prior to enrollment and at days 8 and 15. Owners observed their dogs daily for signs of limping, vomiting, diarrhea, or adverse reactions. The palatability of meloxicam was determined by its acceptance on the food. Hematology and serum chemistry values were evaluated prior to enrollment, and at days 8 and 15.

(d) *Results:* Investigators evaluated lameness, weight bearing, and palpation pain. The results show that in the affected limb, the meloxicam treated group resulted in statistically significant improvement in lameness score at days 8 and 15 ($p=0.0080$, $p=0.0153$ for day 8 and day 15, respectively), palpation pain score at days 8 and 15 ($p=0.0048$, $p=0.0271$ for day 8 and day 15, respectively) and weight bearing score at day 15 ($p=0.0257$).

Percentage of Improvement in Affected Limb Scores

Variable	Day 8			Day 15		
	Meloxicam	Placebo	P-Value	Meloxicam	Placebo	P-Value
Lameness	(56/99) 56.6%	(39/104) 37.5%	0.0080	(66/98) 67.4%	(51/102) 50.0%	0.0153
Weight bearing	(39/99) 39.4%	(32/104) 30.8%	0.2325	(50/98) 51.0%	(36/102) 35.3%	0.0257
Palpation pain	(54/99) 54.6%	(36/104) 34.6%	0.0048	(57/98) 58.2%	(43/102) 42.2%	0.0271

Both investigators and owners assessed overall clinical improvement. The results show that the meloxicam treated group resulted in statistically significant improvement in both investigator and owner clinical evaluations at days 8 and 15 ($p<0.05$).

Percentage of Improvement

	Day 8	Day 15

	Meloxicam	Placebo	P-Value	Meloxicam	Placebo	P-Value
Investigator Evaluation	(44/99) 44.4%	(31/104) 29.8%	0.0457	(59/98) 60.2%	(38/102) 37.3%	0.0027
Owner Evaluation	(52/99) 52.5%	(30/104) 28.9%	0.0010	(60/98) 61.2%	(33/102) 32.4%	0.0001

In addition to assessing an overall clinical improvement of dogs, owners also evaluated their dog's ability to rise, mobility, and lameness. The results show that compared to the placebo group, the meloxicam treated group resulted in statistically significant improvement in ability to rise score at day 15, mobility score and limping score at both days 8 and 15 ($p \leq 0.05$).

Percentage of Improvement in Owner's Additional Evaluation

Variable	Day 8			Day 15		
	Meloxicam	Placebo	P-Value	Meloxicam	Placebo	P-Value
Rise	(49/99) 49.5%	(41/104) 39.4%	0.1620	(53/98) 54.1%	(38/102) 37.3%	0.0301
Mobility	(44/99) 44.4%	(28/104) 26.9%	0.0124	(51/98) 52.0%	(31/102) 30.4%	0.0026
Limping	(46/99) 46.5%	(34/104) 32.7%	0.0515	(54/98) 55.1%	(38/102) 37.3%	0.0147

Hematology and serum chemistry parameters were not negatively affected following meloxicam administration.

(e) Palatability: Owner-evaluated palatability of the Metacam® Oral Suspension when it was administered on food was 92% (88 of 96 dogs). There was no statistically significant difference (p=0.1935) in acceptance of the drug between the groups.

When meloxicam was not accepted on food, it was administered directly into the dogs' mouths. Information on salivation and swallowing using this route of administration was available in 46 of 224 dogs. Of these, three meloxicam and four placebo dogs were less willing to swallow the suspension, one meloxicam and two placebo-treated dogs salivated, and one dog in each group expelled the suspension.

(f) Statistical Analysis: Only sites with at least 6 cases were used in the statistical analysis.

A Cochran-Mantel-Haenszel (CMH) test was used for the analyses of the clinical score variables, investigator and owner evaluations, and owner response variables. These score variables were dichotomized and analyzed. A binary variable was created from the individual score variable based on the criterion that at least one unit decrease from the initial score is considered improved. For overall investigator and owner evaluation scores, a binary variable (improved/not improved) was created by combining original scores of 1 and 2 as improved and 3 and 4 as not improved. A non-parametric method (Kruskal-Wallis test) and a log-rank test were used for palatability data analysis.

All statistically significant findings resulted in a p value of less than or equal to 0.05, unless otherwise stated.

(g) Conclusions: This clinical study demonstrated that a single subcutaneous administration of meloxicam at 0.2 mg/kg, followed by once daily oral administration at 0.1 mg/kg, was effective in controlling the signs of pain and inflammation associated with osteoarthritis in dogs. Improvement was noted by Investigators and Owners by day 7, with continuing improvement through 14 days of meloxicam administration. Meloxicam administration on the food or directly into the mouth was well accepted.

(h) Adverse Reactions

Adverse reactions reported during study

Adverse reaction	Meloxicam no. of dogs (total=109)	Placebo no. of dogs (total=115)
Vomiting	32	15
Diarrhea/Soft Stool	15	11
Inappetance	3	0
Bloody Stool	1	0

(2) Field Study #2(6150-0180-00C-027):

Title: A Field Study Evaluating Metacam® Oral Suspension in Clinical Practice for the Control of Pain and Inflammation Associated with Canine Osteoarthritis.

(a) Type of Study: Clinical Study

(b) Investigators:

Investigator	Clinic	City	State	Zip
Dr. Kimberly Collett	The Animal Center	Alliance	NE	69301
Dr. Thomas Liebl	Clinton Parkway Animal	Lawrence	KS	66047
Dr. Barry Burtis	Bay Cities Animal Hospital	Burlington	Canada	L7R1K
Dr. Erin Robinson	Four Rivers Veterinary Clinic	Ontario	OR	97914
Dr. Jerry Rayburn	Carter Animal Hospital	Winter Haven	FL	33881
Dr. Laurie Culbert	VCA-Northside Animal	Danbury	CT	06811
Dr. Don Ernat	Arlington Park Veterinary	Rolling	IL	60008
Dr. Gary Zinderman	Juno Beach Animal Hospital	Juno Beach	FL	33408
Dr. Edward Jezbera	Riverside Animal Hospital	Riverside	CA	92506

(c) General Design

1 Purpose: The primary objective of this study was to clinically evaluate the safety and effectiveness of Metacam® Oral Suspension in the control of pain and inflammation

associated with canine osteoarthritis (OA). This study further evaluated the palatability of Metacam® Oral Suspension administered directly into the mouth or onto the food.

2 Test Animals : Eighty-two client owned dogs, ranging in age from 6 months to 16 years, and 8 to 140 pounds body weight, were enrolled into this study.

3 Controls: Placebo (similar to meloxicam suspension, except meloxicam active ingredient was omitted).

4 Diagnosis: Dogs with a unilateral or bilateral lameness were eligible for enrollment. The diagnosis of OA was based upon demonstration of at least two of the following clinical signs; a) Pain on palpation of affected joint, b) Unwillingness to use affected joint, c) Swelling of affected joint, d) Perceptible heat over affected joint, e) Crepitus of affected joint, or f) Stiffness of affected joint when rising. Radiographic evidence of osteoarthritis must also have been present; 1 = Radiographic evidence of instability (swollen joint, thickened capsule; no degenerative change), 2 = Mild degenerative change (occasional osteophytes), 3 = Moderate degenerative change (osteophytes, subchondral sclerosis) or 4 = Severe degenerative change (osteophytes, subchondral sclerosis, remodeling of bone).

5 Dosage Form: Final formulation of Metacam® Oral Suspension (1.5 mg/ml)

6 Route of Administration: Oral

7 Dosages Used: Initial oral dose of 0.2 mg/kg body weight on day one, followed by 0.1 mg/kg orally once daily.

8 Treatment Duration: The treatment was administered once daily for a total of 14 days.

9 Parameters Measured: The dogs were examined on day 1 (enrollment), day 8 (interim) and day 15 (final). The primary parameters consisted of three components: lameness, weight bearing, and pain upon palpation. The range for each of the three components was 1 to 5, with one being normal.

Lameness:

The dog was observed both standing and walking. An assessment of both the lame leg and the contralateral limb was made using the following scoring system:

1 = stands and walks normally
2 = stands normally with slight lameness when walking
3 = stands normally with obvious lameness when walking
4 = abnormal stance with slight lameness when walking
5 = abnormal stance with obvious lameness when walking

Weight Bearing:

The dog was observed both standing and walking. An assessment of both the lame leg and the contralateral limb was made using the following scoring system:

1 = normal weight bearing on all limbs at rest and when walking
2 = normal weight bearing at rest. Partial weight bearing when walking
3 = partial weight bearing at rest and when walking
4 = partial weight bearing at rest and non-weight bearing when walking
5 = non-weight bearing at rest and when walking

Pain on Palpation:

The investigator palpated and manipulated the affected area and scored the dog's response according to the following list of responses. An assessment of both the lame leg and the contralateral limb were made:

1 = no response detectable to manipulation of the limb
2 = mild response to manipulation, turns head toward limb
3 = moderate response to manipulation, withdraws limb
4 = severe pain response to manipulation, vocalizes or becomes aggressive

At the 8 and 15 day rechecks, the Investigators and Owners each evaluated the dog's overall condition. Investigators categorized each dog's clinical condition as Excellent, Good, Fair, or Poor Improvement. Owners categorized their dog's overall condition as Greatly, Moderately, Slightly or Not Improved. The Owners also evaluated their dog's ability to rise, mobility and limping prior to enrollment and at days 8 and 15. Owner's observed their dogs daily for signs of lameness, vomiting, diarrhea, or adverse reactions. The palatability of Meloxicam Oral Suspension was determined by its acceptance on the food. Hematology and serum chemistry values were evaluated prior to enrollment, and at days 8 and 15.

(d) *Results:* Investigators evaluated lameness, weight bearing and palpation pain. The results show that in the affected limb, the meloxicam treated group showed clinical improvement, but not statistically significant improvement in lameness score ($p>0.05$), weight bearing score ($p>0.05$), or palpation pain score ($p>0.05$) at either day 8 or day 15.

Percentage of Improvement in Affected Limb Scores

Variable	Day 8			Day 15		
	Meloxicam	Placebo	P-Value	Meloxicam	Placebo	P-Value
Lameness	(20/42) 47.6%	(9/32) 28.1%	0.1256	(23/42) 54.7%	(14/32) 43.8%	0.3518
Weight bearing	(13/42) 31.0%	(10/32) 31.3%	0.9280	(19/42) 45.2%	(9/32) 28.1%	0.1840
Palpation pain	(18/42) 42.9%	(12/32) 37.5%	0.7153	(22/42) 52.4%	(13/32) 40.6%	0.4062

Both investigators and owners assessed overall clinical improvement. The results show the meloxicam treated group resulted in statistically significant improvement only in investigator clinical evaluations at day 8 ($p<0.05$), and owner evaluation at day 15 ($p<0.05$).

Percentage of Improvement

	Day 8			Day 15		
	Meloxicam	Placebo	P-Value	Meloxicam	Placebo	P-Value
Investigator Evaluation	(20/42) 47.6%	(7/32) 21.9%	0.0245	(25/42) 59.5%	(13/32) 40.6%	0.1082
Owner Evaluation	(22/42) 52.4%	(11/32) 34.4%	0.1116	(29/42) 69.1%	(13/31) 42.0%	0.0280

In addition to assessing an overall clinical improvement of dogs, owners evaluated their dog's ability to rise, mobility and lameness. The results show that compared to the placebo group, the meloxicam treated group resulted in statistically significant improvement only in ability to rise score at days 8 and 15 ($p<0.05$), but not in mobility or lameness score at either day 8 or 15 ($p>0.05$).

Percentage of Improvement in Owner's Additional Evaluation

Variable	Day 8			Day 15		
	Meloxicam	Placebo	P-Value	Meloxicam	Placebo	P-Value
Rise	(25/42) 59.5%	(11/32) 34.4%	0.0302	(27/42) 64.3%	(11/31) 35.5%	0.0116
Mobility	(17/42) 40.5%	(7/32) 21.9%	0.1097	(21/42) 50.0%	(9/31) 29.0%	0.1005
Limping	(22/42) 47.6%	(14/32) 43.8%	0.7193	(24/42) 57.1%	(12/31) 38.7%	0.1836

Hematology parameters were not affected following meloxicam administration. Four meloxicam and two placebo dogs had a serum ALT greater than two times the reference range upper limit at the end of the study.

(e) Palatability: Owner-evaluated meloxicam palatability when it was administered on food was 87% (35 of 40 dogs). Palatability results for the second day of the study show that there was no statistically significant difference ($p=0.5707$) between the meloxicam and placebo-treated groups. When meloxicam was not accepted on the food, it was administered directly into the dogs' mouths. Of these dogs, two meloxicam and three placebo-treated dogs were reluctant to swallow the suspension, two other meloxicam dogs drooled after the suspension was given, and another meloxicam dog expelled the suspension.

When meloxicam was given by the investigators, all dogs swallowed the initial dose, although one meloxicam dog and three placebo-treated dogs salivated post-dosing. Owner administration in this manner showed no differences between meloxicam and placebo groups with regard to drooling ($p>0.05$), swallowing ($p>0.05$) or spitting out ($p>0.05$) meloxicam.

(f) Statistical Analysis: Only sites with at least 6 cases were used in the analysis. A Cochran-Mantel-Haenszel (CMH) test stratified by site was used for the analyses of clinical score variables, investigator and owner evaluations, and owner response variables. These score variables were dichotomized and analyzed. A binary variable was created from the individual score variable based on the criterion that at least one unit decrease from the initial score was considered improved. For investigator's clinical score and overall owner evaluation score, a binary variable (improved/not improved) was created by combining original scores of 1 and 2 as improved and 3 and 4 as not improved. A non-parametric method (Kruskal-Wallis test) and a log-rank test were used for palatability data analysis.

All statistically significant results resulted in a p value of less than or equal to 0.05, unless otherwise stated.

(g) Conclusions: This clinical study demonstrated that oral administration of meloxicam at 0.2 mg/kg initially, followed by once daily administration at 0.1 mg/kg, was clinically effective in controlling the signs of pain and inflammation associated with osteoarthritis in dogs. Administration of meloxicam on the food or directly into the mouth was well accepted by the dogs. The study also provided safety information for meloxicam when administered once daily for 14 days.

(h) Adverse Reactions:

Adverse reaction	Meloxicam no. of dogs (total=48)	Placebo no. of dogs (total=34)
Vomiting	8	8
Diarrhea/Soft Stool	3	2
Inappetance	2	1
Bleeding gums after dental procedure	1	0
Lethargy/Swollen Carpus	1	0
Epiphora	1	0

3. TARGET ANIMAL SAFETY

a. Safety Study #1 (06K/83):

(1) Title: Study Of The Parenteral Tolerance Of Substance UH-AC 62 XX In Dogs.

(2) Type of Study: Acute Toxicity (report dated December 22, 1983)

(3) *Investigator:* Dr. R. Serbedija
Karl Thomae GmbH
Experimental Pathology Department
Biberach, Germany

(4) General Design:

(a) Purpose: To determine the toxicological effects of increasing dosages of meloxicam administered to dogs.

(b) Test Animals: Four purebred beagle dogs, 2 males and 2 females, were used in this study. At commencement of treatment the animals were between 9 and 13 months of age and weighed between 11.3 and 14.0 kg.

(c) Dosage Form: Injectable (not final formulation)

(d) Placebo Control: none

(e) Doses Used:

Dose (mg/kg/day)	Relative to Label Dose
2	10 - 20X
6	30 - 60X
12	60 - 120X

(f) Route of Administration: Intravenous

(g) Treatment Duration: Meloxicam was injected 5 times in each dog, with a 2 week interval between each injection (injections occurred during weeks 1, 3, 5, 7 and 9). The meloxicam dosage was increased as the study progressed. The first and second dosages were 2 mg/kg; the third and fourth injections were 6 mg/kg and the final dosage was 12 mg/kg.

(h) Parameters Measured:

- General behavior
- Body weight
- Food consumption
- Rectal temperature
- Heart rate
- Electrocardiogram
- Blood pressure
- Respiratory rate
- Fecal occult blood
- Hematology
- Plasma histamine levels
- Gross pathology
- Histopathology

(5) Results: None of the animals died before the end of the study. The general condition of the dogs deteriorated during the course of the study. The frequency of vomiting increased during the course of the study. During the final week of the study, vomiting occurred frequently and

the animals were lethargic and recumbent. The occurrence of fecal occult blood was highest during the weeks in which the treatments were administered, and increased in frequency and severity during the course of the study corresponding with increases in dosages. Decreases in blood pressure were attributed to the presence of kollidon in this formulation. Kollidon is known to cause histamine release, leading to vasodilation and hypotension. Food consumption and body weight decreased over the period of the study. There were no treatment related effects on heart rate or rhythm. Hematology parameters were stable over the period of the study. On necropsy, gastric ulceration was observed in the pyloric region of all four animals, and was confirmed on histopathology. One of these 4 animals had a perforated pyloric ulcer.

(6) Conclusions: The acute administration of meloxicam to dogs at dosages 60 to 120 times the initial and maintenance dosages (0.2 and 0.1 mg/kg) resulted in signs typical of non-steroidal anti-inflammatory compounds. Gastrointestinal toxicity was the primary effect observed in this study.

b. Safety Study #2 (P98-BIVI015):

(1) Title: Metacam® Oral Suspension (Meloxicam) Target Animal Safety Study by Oral Administration to Beagle Dogs for 42 Days.

(2) Type of Study: Six Week Oral Toxicity

(3) Investigator: Thomas G. Smith
Huntingdon Life Sciences Ltd.
Wooley Road, Alconbury
Huntingdon, Cambridgeshire, PE28 4HS, England

(4) General Design:

(a) Purpose: To determine the toxicological effects of oral doses of Metacam® Oral Suspension administered once daily for six weeks.

(b) Test Animals: Twenty four purebred beagle dogs were divided into four groups each of 3 males and 3 females. At commencement of treatment, the animals were between 11 and 12 months of age and weighed between 9.3 and 14.8 kg.

(c) Dosage Form: Oral Suspension

(d) Placebo Control: Physiological saline

(e) Doses Used:

Dose (mg/kg/day)	Relative to Label Maintenance Dose
0	0X
0.1	1X
0.3	3X
0.5	5X

(f) Route of Administration: Oral

(g) Treatment Duration : 6 weeks

(h) Parameters Measured:

- General health observations
- Body weight
- Food consumption
- Water consumption
- Rectal temperature
- Hematology
- Blood chemistry
- Urinalysis
- Fecal occult blood
- Gross pathology
- Histopathology

(5) Results: Mild, sporadic vomiting or diarrhea were observed in the control and two treatment groups. Two dogs in the control group exhibited one episode of vomiting or diarrhea during the 42 day study. In the 1X group, one dog had three episodes of diarrhea, one had one episode of vomiting and diarrhea, and one dog had two episodes of vomiting while receiving meloxicam. In the 5X group, one dog had one occurrence of diarrhea, one had two occurrences of vomiting, and one had one occurrence of diarrhea while receiving meloxicam. There were no occurrences of vomiting or diarrhea in the 3X dogs. Occult fecal blood was not detected in any dogs at any time during the study.

Macroscopic changes noted following the administration of meloxicam were areas of congestion or depression on the mucosa of the jejunum or ileum in three individual dogs receiving 1X and two dogs receiving 5X. Similar changes were also seen in two dogs in the control group. No changes were observed in the 3X group. Microscopic evaluation of these changes consisted of necrosis and some inflammatory cell infiltration affecting adjacent villi. Microscopic examination of the kidneys detected necrosis of the tip of the papilla in one 5X dog, and degeneration in two 5X dogs. No renal lesions were found in the 1X or 3X groups.

Changes in other parameters were not clinically significant.

(6) Conclusions: The oral administration of meloxicam to dogs for 42 days at 0.1, 0.3 and 0.5 mg/kg/day was well tolerated. Clinical signs consistent with non-steroidal anti-inflammatory administration, vomiting and diarrhea, were observed. Grossly, mucosal petechiae were observed in one control, two 3X dogs and one 5X dog. On histology, only one dog in the 5X group demonstrated renal changes characterized as minimal to slight papillary necrosis, while two dogs in this group demonstrated minimal degeneration of the tip of the papilla. These changes are consistent with non-steroidal anti-inflammatory drug toxicity. Gastrointestinal macroscopic lesions were limited to congestion and depression of the jejunal and ileal mucosa in two dogs in the control group, in three dogs in the 1X group, and two dogs in the 5X group. Histology of these lesions showed no evidence of ulceration.

Meloxicam administered for a period of 42 days was well tolerated by these dogs. Clinically relevant signs included vomiting and diarrhea in the 1X and 3X groups, with mucosal congestion and depressions present in the 1X and 5X group on necropsy.

c. Safety Study #3 (6150-0987-00C-06):

(1) Title: 26-Week Oral (Liquid) Toxicity Study in the Beagle Dog on Metacam® Oral Suspension.

(2) Type of Study: Six-Month Oral Toxicity

(3) Study Director: Donald C. Emmerling
Battelle Pharmaceutical Product Development
505 King Avenue
Columbus, Ohio 43201-2693

(4) General Design:

(a) Purpose: To determine the safety of Metacam® Oral Suspension in dogs following 26-weeks of oral administration.

(b) Test Animals: Twenty-four purebred beagle dogs were divided into four groups, each with 3 males and 3 females. At commencement of treatment, the animals were between 8 and 10 months of age and weighed between 6.8 and 12.0 kg.

(c) Dosage Form: Oral Suspension

(d) Vehicle Control: Identical to test material without active ingredient.

(e) Doses Used:

Initial Dose (mg/kg) Day 1 only	Maintenance Dose (mg/kg/day) Days 2 - 182	Relative to Label Dose
0	0	
0.2	0.1	1X
0.6	0.3	3X
1.0	0.5	5X

(f) Route of Administration: Oral

(g) Treatment Duration : 26 weeks

(h) Parameters Measured: Clinical observations were made on all dogs twice daily.

- body weight
- food consumption
- clinical pathology (hematology and serum chemistry parameters)
- urinalysis
- physical examinations
- ophthalmic examinations
- endoscopic examinations
- clotting time
- buccal mucosal bleeding time
- Plasma meloxicam levels (on Day 1 and during Weeks 7, 14 and 26)
- Gross pathology
- histopathology

(5) Results: The most common clinical abnormalities seen in this study were interdigital cysts, gastrointestinal distress (diarrhea and vomiting), and clear ocular discharge. The occurrences of these findings were similar among meloxicam-treated and control-treated dogs. Reddened feces was observed in one control, one 1X and two 3X dogs. No other abnormalities were found during physical examinations.

There were treatment-related changes observed in hematology and clinical chemistry. Decreased red blood cell counts were seen in four 3X and three 5X dogs. On Day 22, the values for one dog in each group fell outside the reference range. Overall, the red blood cell counts were statistically significantly lower in the 5X group when compared to those of the control group ($p=0.043$). Low hematocrit values (34%) were seen only in one 3X dog. Overall, the hematocrit was statistically significantly lower ($p=0.052$) on days 22, 79 and 176 in the 3X dose group, and over the study time period (except day 121) in the 5X dose group when compared to the control group. There was evidence of regenerative anemia (decreased red blood cell count, hematocrit and hemoglobin with increased mean corpuscular volume) in two 3X and one 5X dogs. A dose-related neutrophilia over time was seen in one 1X, two 3X

and three 5X dogs. Also noted were increasing (but still within reference range) BUN values in two 5X dogs. Decreased albumin values were also observed in one 5X dog (3.2 to 2.7 g/dL). Albumin was noted to be statistically significantly lower (p=0.015) on day 176 in the 3X dose group, and on days 22, 51 and 176 in the 5X dose group.

There were no clinically or statistically significant changes in coagulation parameters (PT, APTT, Lee-White Clotting Time or Buccal Mucosal Bleeding Times) identified during the study.

Endoscopic examinations were performed pre-study and at 2, 8, 18, and 26 weeks. Redness covering less than 25% of the surface area of the gastric mucosa was seen in two controls, three 1X, three 3X, and two 5X dogs. Two dogs receiving placebo showed redness covering less than 25% of the surface area in conjunction with areas of ulceration of the gastric mucosa. Of the dogs with endoscopic changes, only one dog in the 5X group exhibited red foci of the fundic mucosa at necropsy. However, no histologic changes were observed.

In the urinalyses, bilirubin was present in the urine of one 5X dog during all treatment timepoints. Bilirubin was present sporadically in the urine of two control dogs, three 1X dogs, two 3X dogs and one 5X dog.

Macroscopic changes were observed in four dogs administered meloxicam. One dog in the 1X group had multifocal pinpoint red foci in the stomach. One dog in the 3X group had discoloration of the gastric mucosa and hepatic capsular fibrosis. Two dogs in the 5X group had minimal red foci in the stomach and mild red discoloration of the duodenum near the pylorus, respectively. For one dog in the 3X group, there were correlating microscopic changes observed, which were characterized as mild focal congestion in the fundus.

(6) Statistics: Quantitative variables measured at several times (feed consumption, body weight, hematology, serum chemistry and urinalysis parameters) during treatment period were analyzed using analysis of covariance for repeated measures with main effects of treatment, gender and time, along with all interaction effects of these main effects. The mean of the pretreatment values was included as a covariate in the analysis.

The appropriate structure (CS, or AR(1), or ARH(1)) for the covariance matrix was assessed in the analysis of the representative parameter from each type of the variable.

Least-square treatment means were computed for each dose level, each gender, and at each time point for the post-treatment period.

If overall treatment effect or the time by treatment interaction effect was statistically significant ($p<=0.10$), then the variation in the treatment means was further evaluated using application of Fisher's least-significant-difference (LSD) method to compare the means among dose groups or the means among dose groups at each time point. If the gender by treatment interaction effect was statistically significant ($p<=0.05$), the means among dose groups were compared within gender.

Additionally, if the interaction "dose by time" was statistically significant, the least-squares means for each dose group at each measurement time were plotted.

(7) *Conclusions:* The oral administration of meloxicam to dogs for 26 weeks at the 0.1 mg/kg/day dose was found to be safe. Typical non-steroidal anti-inflammatory drug-related effects were seen at the 0.3 and 0.5 mg/kg/day doses. These effects included abnormalities in red blood cell counts, hematocrit, and neutrophil counts. There was also evidence of regenerative anemia, increasing BUN, and decreased albumin. Despite the presence of bilirubin in the urine of several dogs, there was no associated liver pathology or evidence of clinical disease; therefore, the relevance of this finding is unknown. Clinical observations consistent with non-steroidal anti-inflammatory drug administration were seen in this study and included diarrhea and vomiting.

4. HUMAN SAFETY:

Human Safety Relative to Food Consumption:

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, data on human safety pertaining to drug residues in food were not required for approval of this NADA.

Human Safety Relative to Possession, Handling and Administration:

Labeling contains the following adequate warnings: "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. For oral use in dogs only."

5. AGENCY CONCLUSIONS:

Data in support of this NADA comply with the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act and Section 514.1 of the implementing regulations. The data demonstrate that Metacam® Oral Suspension (meloxicam), when administered according to labeled conditions of use, is safe and effective for the control of pain and inflammation associated with osteoarthritis in dogs.

Metacam® Oral Suspension (meloxicam) is restricted to use by or on the order of a licensed veterinarian because professional veterinary expertise is required to determine when a dog has a condition such as osteoarthritis, and to monitor the dog for signs of adverse reactions.

Under section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of the approval because no active ingredient of the new animal drug has previously been approved.

Meloxicam is under the following U.S. patent number:

U.S. Patent Number	Date of Expiration

6. ATTACHMENTS:

Facsimile Labeling is attached as indicated below:

a. package insert for 0.5 mg/mL concentration
b. client information sheet for 0.5 mg/mL concentration
c. bottle label for 15 mL container of 0.5 mg/mL concentration
d. bottle label for 30 mL container of 0.5 mg/mL concentration
e. carton label for 15 mL container of 0.5 mg/mL concentration
f. carton label for 30 mL container of 0.5 mg/mL concentration
g. shipping label for 15 mL container of 0.5 mg/mL concentration
h. shipping label for 30 mL container of 0.5 mg/mL concentration

i. package insert for 1.5 mg/mL concentration
j. client information sheet for 1.5 mg/mL concentration
k. bottle label for 10 mL container of 1.5 mg/mL concentration
l. bottle label for 32 mL container of 1.5 mg/mL concentration
m. bottle label for 100 mL container of 1.5 mg/mL concentration
n. carton label for 10 mL container of 1.5 mg/mL concentration
o. carton label for 32 mL container of 1.5 mg/mL concentration
p. carton label for 100 mL container of 1.5 mg/mL concentration
q. shipping label for 10 mL container of 1.5 mg/mL concentration
r. shipping label for 32 mL container of 1.5 mg/mL concentration
s. shipping label for 100 mL container of 1.5 mg/mL concentration