Approval Date: November 12, 2003

FREEDOM OF INFORMATION SUMMARY

NEW ANIMAL DRUG APPLICATION

NADA 141-219

METACAM (meloxicam) 5 mg/mL Solution for Injection

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

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

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FREEDOM OF INFORMATION SUMMARY

1. *GENERAL INFORMATION*

a. File Number:	NADA 141-219
b. Sponsor:	Boehringer Ingelheim Vetmedica, Inc. 2621 North Belt Highway St. Joseph, Missouri 64506 Drug Labeler Code: 000010
c. Established Name:	Meloxicam
d. Proprietary Name:	METACAM (meloxicam) 5 mg/mL Solution for Injection
e. Dosage Form:	Meloxicam is an injectable 5.0 mg/mL sterile solution.
f. How Supplied:	10 mL multiple dose vials
g. How Dispensed:	Rx
h. Amount of Active Ingredients:	5.0 mg/mL meloxicam solution
i. Route of Administration:	Intravenous or subcutaneous injection
j. Species/Class:	Dogs
k. Recommended Dosage:	METACAM 5 mg/mL Solution for Injection should be administered initially as a one-time dose at 0.2 mg/kg body weight intravenously or subcutaneously. Continue with METACAM Oral Suspension after 24 hours at a daily dose of 0.1 mg/kg body weight, either mixed with food or placed directly into the mouth.
l. Pharmacological Category:	Non-Steroidal Anti-Inflammatory (NSAID)
m. Indications:	METACAM (meloxicam) 5 mg/mL Solution for Injection 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 with 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 loading 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 pain on palpation. 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*

A study was conducted to demonstrate the effectiveness of METACAM (meloxicam) in dogs for the control of pain and inflammation associated with osteoarthritis. This field study was conducted in various locations. Results of this study demonstrate that meloxicam is effective when administered at an initial dose of 0.2 mg/kg body weight intravenously (IV) or subcutaneously (SQ) followed by 0.1 mg/kg body weight orally.

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

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

(a) *Type of Study:* Field Study

(b) *Investigators:*

	City	State/Province
Dr. Wallace Diehl	Chapel Hill	NC
Dr. Barbara Teter	Omaha	NE
Dr. David Knaak	Bartonville	IL
Dr. Robert Wilbanks	San Antonio	TX
Dr. Dean Vicksman	Denver	CO
Dr. Lori Teller	Houston	TX
Dr. Valerie Kastens	Salt Lake City	UT
Dr. LD Eckermann	Houston	TX
Dr. Timothy Munjar	Beaverton	OR
Dr. Kimberly Collett	Alliance	NE
Dr. Kevin Taylor	Peoria	IL
Dr. William H. Craig	San Antonio	TX
Dr. Christopher Rodi	Oceanside	CA
Dr. Thomas Liebl	Lawrence	KS
Dr. Barry Burtis	Burlington	Ontario, Canada
Dr. Peter Grinberg	Kitchener	Ontario, Canada
Dr. Joy Courey	Brampton	Ontario, Canada
Dr. Amanda Glew	Hudson	Quebec, Canada
Dr. Erin Robinson	Ontario	OR
Dr. Jerry Rayburn	Winter Haven	FL
Dr. Gerald Ramsdell	North East	PA

(c) *General Design*

1 Purpose: The objectives of this study were: 1) clinically evaluate the safety and effectiveness of meloxicam (METACAM) in 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: METACAM 5 mg/mL Solution for Injection vehicle and METACAM 0.5 mg/mL and 1.5 mg/mL Oral Suspension vehicles (Note that in both the meloxicam solution for injection vehicle and the meloxicam oral suspension vehicle, the 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 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 formulations of METACAM 5 mg/mL Solution for Injection and METACAM 0.5 mg/mL and 1.5 mg/mL Oral Suspensions

6 Route of Administration: Subcutaneous and Oral

7 Dosages Used: Initial subcutaneous dose of meloxicam solution for injection at 0.2 mg/kg on day one, followed by 0.1 mg/kg meloxicam oral suspension orally once daily.

8 Treatment Duration: The meloxicam solution for injection was administered one time followed by 13, once-daily doses of meloxicam oral suspension.

9 Variables 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. The investigators also monitored adverse reactions.

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. Owners observed their dogs daily for signs of limping, vomiting, diarrhea, or adverse reactions. Hematology and serum chemistry values were evaluated prior to enrollment, and at Days 8 and 15.

(d) *Results:* Investigators evaluated lameness, weight bearing, and pain on palpation. 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), pain on palpation 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
Pain on palpation	(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 rise score at Day 15, and 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. Gastrointestinal signs including vomiting, diarrhea, inappetance, and bloody diarrhea were noted in approximately twice the number of meloxicam-treated animals versus placebo-treated animals.

(e) *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.

(f) *Conclusions:* This field study demonstrated that 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.

(g) *Adverse Reactions:*

Adverse Reactions Observed During Field Study

Adverse reaction	Meloxicam no. of dogs (total=109)	Placebo no. of dogs (total=115)
Vomiting	31	15
Diarrhea/Soft Stool	15	11
Inappetance	3	0
Bloody Stool	1	0

3. *TARGET ANIMAL SAFETY:*

a. Study 06K/83

(1) *Title:* Study of the Parenteral Tolerance of Substance UH-AC 62 XX in Dogs.

(2) *Type of Study:* Tolerance

(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 doses of meloxicam administered to dogs.

(b) Test Animals: Four pure bred 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 Dose
2	10x
6	30x
12	60x

(f) Route of Administration: Intravenous

(g) Treatment Duration: All dogs received a total of 5 injections with a 2 week interval between each injection. The first and second injection doses were 2 mg/kg (10x); the third and fourth injections were 6.0 mg/kg (30x) and the final dose was 12 mg/kg (60x).

(h) Variables Measured:

1 General behavior
2 Body weight
3 Food consumption
4 Rectal temperature
5 Heart rate
6 Electrocardiogram
7 Blood pressure
8 Respiratory rate
9 Fecal occult blood
10 Hematology
11 Plasma histamine levels
12 Gross pathology
13 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 doses. 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 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 nonsteroidal anti-inflammatory compounds. Gastrointestinal toxicity was the primary effect observed in this study.

b. Study 6821 UHA 9320

(1) *Title:* Preliminary observations on the local tolerance of the meloxicam injection solution (METACAM) in comparison to a ketoprofen injection solution[1] after subcutaneous injection in healthy dogs.

[1] Ketoprofen is currently not approved for use in dogs in the United States. Therefore, only the meloxicam data from this study is presented in this FOI summary.

(2) *Type of Study:* Experimental Local Tolerance Study

(3) *Investigators:* Dr. K.D. Schulz, G. Maier
D-88397
Biberach an der Riss 1, Germany

(4) *General Design:*

(a) Purpose: To obtain information on the local tolerance of a 0.5% meloxicam injection solution (METACAM) following subcutaneous administration in healthy experimental dogs.

(b) Test Animals: Healthy dogs were selected from a colony of experimental animals for use in this study. The animals were between six months and 7 years of age and weighed between 11.9 and 35.0 kg.

(c) Dosage Form: Final formulation of METACAM 5 mg/mL Solution for Injection

(d) Diagnosis/Inclusion Criteria: Only healthy male and female experimental dogs as assessed by a general clinical examination were included in the study.

(e) Doses Used: METACAM 5 mg/mL Solution for Injection administered once at 0.2 mg/kg body weight

(f) Route of Administration: Subcutaneous

(g) Treatment Duration: All dogs received a single injection with a post-administration observation period of 24 hours.

(h) Variables Measured: Pain reactions and local inflammatory signs were observed both during and post-injection.

(5) *Results:* The results of the study indicated meloxicam injectable solution was well tolerated by the animals. Pain upon injection was observed in 1/8 animals treated with meloxicam. No after treatment pain or local inflammatory signs were observed post-injection from the meloxicam injectable solution.

(6) *Conclusions:* The study provided evidence that 0.5% meloxicam injection solution administered subcutaneously at a dose level of 0.2 mg/kg was well-tolerated locally in dogs and may be recommended as a standard route of administration.

c. Study 635-0180-97C-014

Title: The Effects of Meloxicam (METACAM) on Buccal Mucosal Bleeding Time and a Comparison to Ketoprofen and Butorphanol in Controlling Postoperative Pain in Dogs.

(1) *Type of Study:* Laboratory Study

(2) *Investigators:* Drs. Karol Mathews and Glen Pettifer
Ontario Veterinary College
University of Guelph
Guelph, Ontario, Canada N1G 2W1

(3) *General Design:*

(a) Purpose: The objective of this study was to evaluate the safety of meloxicam administration with regard to buccal mucosal bleeding times.

(b) Test Animals: Twelve female and twenty-four male lab-raised Beagle dogs were used in the study. The dogs ranged in age from 6 to 9 1/2 months of age.

(c) Controls: Saline was used as a negative control.

(d) Diagnosis: These were normal dogs.

(e) Dosage Form: Final formulation of METACAM 5 mg/mL Solution for Injection The control was physiological saline.

(f) Route of Administration: Intravenous

(g) Dose Used: Meloxicam was given at 0.2 mg/kg. Placebo was administered at 0.2 mg/kg.

(h) Treatment Duration: Meloxicam was administered once.

(i) Variable Measured: Buccal Mucosal Bleeding Times (BMBT). The BMBT was performed prior to treatment administration and then at 1, 4, 8, 24, and 48 hours post injection.

(4) *Results:* No clinically significant changes in BMBT were found between the meloxicam or placebo groups.

(5) *Conclusions:* Meloxicam did not significantly alter buccal mucosal bleeding times following intravenous administration.

(6) *Adverse Events:* No adverse events occurred during the study.

d. Study P98-BIVI008 (BOI/200)

Title: Target Animal Safety Study by Intravenous (bolus) Administration to Beagle Dogs for 3 Days

(1) *Type of Study:* Toxicity

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

(3) *General Design:*

(a) Purpose: To determine the toxicological effects of intravenous administration of METACAM solution administered once daily for three days.

(b) Test Animals: Twenty-four pure bred beagle dogs were divided into four groups each, with 3 males and 3 females. The study animals were between 11 and 13 months of age and weighed between 8.5 and 14.3 kg.

(c) Dosage Form: Injectable solution containing 5 mg meloxicam per mL. The final market formulation was used.

(d) Placebo Control: METACAM vehicle

(e) Doses Used:

Dose (mg/kg/day)	Relative Dose
0	0x
0.2	1x
0.6	3x
1.0	5x

(f) Route of Administration: Intravenous injection

(g) Treatment Duration: 3 days

(h) Variables Measured: General health observations (clinical signs), body weight, food consumption, water consumption, and rectal temperature were recorded at various points during the acclimation period and daily for Days 1-4. Hematology and serum chemistry were collected on Days -8 and Days 1-4. Urinalysis samples were obtained on Days -8, 1 and 4. Fecal occult blood samples were collected on Days -2, 1, -1, and Days 1-4. All observations or samplings for Day 4 were completed prior to necropsy. Gross pathology was noted and tissues were collected for histopathological evaluation at time of necropsy on Day 4.

(4) *Results:*

(a) Clinical Signs

Vomiting occurred in one 1x and one 5x dog on Day 3. Fevers were observed in a total of five dogs, one each in the 1x and 3x groups, and three in the 5x treatment group. Occult fecal blood was observed on Day 3 in three 5x dogs.

(b) Hematology/Serum Chemistry/Urinalysis

Increased white blood cell counts were seen in one 1x, three 3x and five 5x dogs. Of these, two 3x and three 5x dogs had stress leukograms (neutrophilia, monocytosis, +/- eosinophilia, +/- lymphopenia) on bloodwork. The PCV remained normal in dogs during the study. Mild platelet decreases were noted in two 3x and four 5x dogs. The PT and APTT values were within the normal reference range.

Liver enzyme changes were observed during the study. Serum ALP was clinically significantly increased in four 3x and two 5x dogs. Elevations in GGT were noted in one control, two 1x, one 3x, and two 5x dogs, but these remained all within normal reference range limits.

Decreased serum total protein was seen in two 3x and three 5x dogs. One of the 5x dogs developed acute renal failure by the end of the study. A statistically significant "dose by gender" effect was seen in the 5x group on days 3 and 4 for both albumin ($p=0.0993$ and $p=0.0256$, respectively) and albumin/globulin ratios ($p=0.0981$).

Increased BUN was seen in three 1x, two 3x and three 5x dogs. Above normal reference range BUN values were seen in one 5x dog (Normal =10-30 mg/dL, 5x dog=60 mg/dL) on day 4. Clinically significant changes in creatinine were seen in two

5x dogs. Both of these female dogs developed acute renal failure (ARF) by day 4 of the study.

Changes in electrolytes were noted, including marked elevations in serum calcium in two 5x dogs, and milder elevations in two 1x dogs. A decreased chloride was noted in one 5x dog on day 4, most likely due to protracted vomiting on day 3. Increased bicarbonate was seen in one control, two 3x and one 5x dog. The 5x dog's values were highest on day 4, when she developed acute renal failure.

Urinalysis changes included decreased urine specific gravity in the one 5x dog which developed ARF. Clinically significantly increased urine protein concentration was seen in both of the 5x ARF dogs. Hemoglobinuria was seen in two 5x dogs on day 4.

(c) Gross Necropsy Observations

Female dogs in the 1x group had areas of congestion, inflammation and hemorrhage in the colon, ileum, and cecum. Dogs in the 3x group experienced pyloric mucosal hemorrhages and pyloric mucosal erosions. Areas of mucosal congestion were observed in the jejunum and ileum in four of the 5x dogs. These findings are considered drug-related.

(d) Histologic Observations

Microscopic renal changes, consisting of bilateral necrosis of the tip of the papilla, were seen in all three females of the 5x group. These changes were graded as slight in two of these dogs, and minimal in the other. Two of these dogs also showed dilated cortical and medullary tubules, graded as slight and moderate respectively. One 5x female had macroscopically enlarged kidneys and swollen/vacuolated epithelial cells in the cortical tubules on histopathology. These renal changes are considered treatment related. Similar findings were not noted in any males receiving 5x. Renal changes were noted in the 1x and 3x groups but were not as severe as those of the 5x group.

Microscopic mucosal erosion was seen in the small intestine in three animals receiving 5x. Two females showed slight areas of mucosal erosion in the jejunum, and one male showed mucosal erosion over the gut-associated lymphoid tissue (GALT) in the ileum. All three dogs were positive for occult fecal blood on Days 3 or 4 of the study.

Hepatocyte cytoplasmic rarefaction with vacuolation was seen in dogs of the 3x group. No other hepatic histologic changes were found in any of the other dogs.

(5) *Statistical Analysis:*

For all variables, males and females were analyzed separately and combined.

Levene's test for homogeneity was applied. If the test was significant at the 1% level, then a logarithmic transformation was applied and the test was repeated. If Levene's test was still significant, than a square root transformation was tried.

Except for organ weights, if no significant heterogeneity of variance was detected (with or without transformation), a one-way analysis of variance was carried out, using treatment as a factor. If the analysis of variance showed evidence (at the 10% level) of differences between the groups, then a two-sided Dunnett's test was used to compare the treated groups with the controls group. Significance testing was carried out at the 5% and 1% levels.

If heterogeneity of variance was significant and could not be stabilized by transformation, then the Kruskal-Wallis test on ranks was performed on the transformed data. If the Kruskal-Wallis test showed evidence (at the 10% level) of differences between the groups, then, for the combined sexes, the Wilcoxon Rank Sum test was used to test for differences between the treated groups and the control, whilst for the separate sexes, Steel's test (a non-parametric analogue of Dunnett's test) was used.

For absolute organ weights, an analysis of covariance was performed, adjusting for the final body weight where the regression coefficient describing the linear relationship between organ weight and the covariate was significantly different from zero at the 10% level. Where there was no such relationship, analysis of variance was performed on the unadjusted values as described above. If the analysis of covariance was applied, and if a significant difference (at the 10% level) was found between the groups, the groups were compared using Dunnett's test.

(6) *Conclusions:*

Treatment-related effects were observed in all meloxicam treatment groups as evidenced by changes in serum chemistry, occult fecal blood, and gross and histopathological lesions. The treatment related effects were least severe in the 1x group and most severe in the 5x group.

This study demonstrated that meloxicam was safe when administered at the therapeutic (1x) level, but that toxicity increased at higher doses.

(7) *Adverse Reactions:*

Adverse reactions seen with administration of meloxicam solution for injection are shown in the following table:

Table 1. Adverse Reactions Seen in Study P98-BIVI008 (BOI/200)

Adverse Reaction	Number of Meloxicam Dogs Affected (n=12)	Day of Occurrence	Number of Placebo Dogs Affected (n=12)
Acute Renal Failure	2 dogs (both 5x group)	Day 4	0
Vomiting	2 dogs (one in 1x and one in 5x group)	Day 3	0
Fever	5 dogs (one in 1x, one in 3x and 3 in 5x)	Days 3 and 4	0

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

Human Warnings are provided on the product label as follows: "Not for use in humans. Keep this and all medications out of the reach of children. Consult a physician in case of accidental ingestion by humans."

5. *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 of the implementing regulations. The data demonstrate that METACAM (meloxicam) 5 mg/mL Solution for Injection when administered according to labeled conditions is safe and effective for the control of pain and inflammation associated with osteoarthritis in dogs.

METACAM 5 mg/mL Solution for Injection (meloxicam) is restricted to use by or on the order of a licensed veterinarian because professional 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)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of approval. This NADA contains a target animal safety study as well as a dose confirmation study and a field study to satisfy the requirements for substantial evidence of effectiveness.

6. ATTACHMENTS:

Facsimile Labeling is attached as indicated below:

a. package insert for 5.0 mg/mL concentration
b. vial label for 10 mL container of 5.0 mg/mL concentration
c. carton label for 10 mL container of 5.0 mg/mL concentration
d. shipping label for 10 mL containers of 5.0 mg/mL concentration