Approval Date: August 21, 2002

FREEDOM OF INFORMATION SUMMARY

NADA 141-203

DERAMAXX™ Chewable Tablets
(deracoxib)

" for the control of postoperative pain and inflammation associated with orthopedic surgery in dogs."

Sponsored by: Novartis Animal Health US, Inc.
3200 Northline Avenue Suite 300
Greensboro, NC 27408

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FREEDOM OF INFORMATION SUMMARY

I. General Information

A. File Number: 141-203

B. Sponsor: Novartis Animal Health US, Inc
3200 Northline Avenue Suite 300
Greensboro, North Carolina 2740

C. Established Name: deracoxib

D. Proprietary Name: DERAMAXX™ Chewable Tablets

E. Dosage Form: scored, flavored tablets

F. How Supplied: The product is available as 25 mg and 100 mg round, brownish, half-scored tablets in 7, 30, and 90 count bottles.

G. How Dispensed: Prescription (Rx) – US Federal law restricts this drug to use by, or on the order of, a licensed veterinarian.

H. Amount of active ingredient: Each tablet contains 25 mg or 100 mg of deracoxib.

I. Route of Administration: oral

J. Species/Class: dogs

K. Recommended Dosage: The recommended daily dose of DERAMAXX tablets for postoperative orthopedic pain is 3-4 mg/kg/day (1.4 to 1.8 mg/lb/day) as a single daily dose, as needed for 7 days. Tablets are scored and dosage should be calculated in half-tablet increments.

L. Pharmacological Category: Non-steroidal anti-inflammatory drug (NSAID)

M. Indications: DERAMAXX™ Chewable Tablets are indicated for the control of postoperative pain and inflammation associated with orthopedic surgery in dogs $\geq$ 4 lbs (1.8 kg).

II. Effectiveness

A. DOSAGE CHARACTERIZATION:

A once daily, oral dose of 3-4 mg/kg of deracoxib was based on the results of a study to evaluate the drug's effectiveness in a surgical model of cranial cruciate ligament repair in dogs. Dogs received deracoxib or a placebo 30 minutes before surgery and once daily for 14 days. Dogs were assigned to a 0, 2, 4, or 6 mg/kg/day group. Pain and lameness assessments were evaluated for each dog in the 4 groups. These evaluations included a clinical assessment of pain and lameness, a measurement of the range of motion in the surgical stifle, and forceplate evaluation.

A subjective and objective baseline evaluation of pain and lameness was made prior to drug administration and at 13 assessment times postoperatively. Pain and lameness scores were statistically significant from the 18^{th} hour post-surgery (assessment #3) through the 24^{th} hour of Day 7 (assessment #9) following administration. Many dogs across all treatment groups were partially or non-weight bearing postoperatively on the affected limb, limiting the collection of sufficient forceplate data.

The average clinical pain and lameness scores for the 4 mg/kg deracoxib group showed statistically significant improvement ($p< 0.05$) within the first day post-surgery (similar improvement was noted in the 2 mg/kg deracoxib group within three days post-surgery). These results support the effectiveness of deracoxib at 4 mg/kg for the control of orthopedic postoperative pain and inflammation.

One dog in the 6 mg/kg/day group was considered a surgical failure (lack of joint stability). The impact of postoperative activity on this dog is unknown. The percentage of pre- to post-study urine samples with detectable levels of bilirubin decreased for all dose groups, with the exception of the 6 mg/kg dose group. The percentage of urine samples in this group with detectable levels of bilirubin increased from 0 to 20%. Pre-surgical cytologic synovial fluid analysis of all dogs showed no evidence of inflammation. Post-surgical cytological analysis revealed varying degrees of neutrophilic inflammation (mild to suppurative) in deracoxib-treated dogs. One synovial sample in the 4 mg/kg deracoxib group cultured positive for *S. aureus*, and one sample in the 6 mg/kg group was suggestive of sepsis, although no culture was done.

Summary Conclusion: Clinicopathologic abnormalities were identified at 6 mg/kg. Based on evaluation of the clinical pain and lameness scores, the effective deracoxib dose selected for the control of postoperative orthopedic pain and inflammation is 3-4 mg/kg/day, when given 30 minutes before surgery.

B. SUBSTANTIAL EVIDENCE:

1. Field Study

The effectiveness of DERAMAXX™ Chewable Tablets for the control of postoperative orthopedic pain and inflammation was evaluated in dogs presented for surgical repair of a cranial cruciate ligament injury. The study was conducted at six veterinary clinics throughout the U.S. Results of the study demonstrate that DERAMAXX™ Chewable Tablets are safe and effective when administered at a dose of 3-4 mg/kg of body weight once daily for a maximum of 7 days.

The intensity of surgical pain varied with the duration of the procedure and individual response to pain; therefore, the requirement for pain control may have varied amongst cases.

A variety of drugs was used in conjunction with the surgical procedure. Surgical inductions included the use of combinations of pre-anesthesia medications, barbiturates, inhalant anesthetics, anticholinergics, antibiotics and parenteral fluids.

a. Type of Study: Placebo-Controlled, Masked, Randomized Field Study

b. Investigators:

Michael G. Conzemius, DVM, Dipl. ACVS Veterinary Teaching Hospital Iowa State University Ames, IA 50011-1250	Katherine L. Wells, DVM Metroplex Veterinary Centre 700 Airport Freeway West Irving, TX 75062
Brian S. Beale, DVM, Dipl. ACVS Gulf Coast Veterinary Specialists 1111 West Loop South, Suite 160 Houston, TX 77027	David C. Sweet, VMD, Dipl. ACVS Jill L. Sammarco, BVSc, MRCVS, Dipl ACVS, Dipl. ECVS Veterinary Referral Centre 48 Notch Road Little Falls, NJ 07424
Darryl L. Millis, DVM, Dipl. ACVS College of Veterinary Medicine University of Tennessee Knoxville, TN 37996-4500	Alan J. Lipowitz, DVM, Dipl. ACVS College of Veterinary Medicine University of Minnesota St. Paul, MN 55108

c. General Design:

i) Purpose: The study objective was to evaluate the clinical effectiveness and safety of DERAMAXX tablets at a dose of 3-4 mg/kg orally once daily for 7 days, for the control of postoperative orthopedic pain associated with cranial cruciate ligament repair. The protocol allowed

for a single dose of butorphanol for control of pain, if additional analgesia was warranted in the opinion of the investigator.

ii) Test animals: Two hundred and seven client-owned male and female dogs ranging from 1-15 years of age, representing 43 different breeds were included in the study. A total of 59 dogs treated with deracoxib and 60 dogs that received a placebo were evaluated for effectiveness. One hundred and five dogs treated with deracoxib and 102 dogs that received a placebo were included in the safety evaluation.

iii) Control: The placebo was identical to DERAMAXX tablets without the active ingredient.

iv) Dosage form: DERAMAXX tablets (final market formulation)

v) Route of administration: Oral

vi) Dosage used: 3-4 mg/kg (1.4- 1.8 mg/lb) administered the evening before surgery, then once daily for 6 days postoperatively.

vii) Test duration: 7 days

viii) Parameters measured: Seven days pre-study, and on Days 2, 3, 4, and 7, the investigators assessed each dog for lameness at a walk, lameness at a trot, and pain on palpation of the affected stifle, joint mobility, as well as the need for additional postoperative analgesia.

Prior to the study and again on Day 7, hematology and clinical chemistry samples were obtained.

d. Results: One hundred and nineteen (119) dogs were included in the overall effectiveness analysis. Statistically significant differences ($p< 0.05$) favored deracoxib at all postoperative evaluations for lameness at a walk, lameness at a trot, and pain on palpation scores. See Table 1.

Table 1. Deracoxib vs. Placebo

	P-values of the statistical comparison of deracoxib vs. placebo		
Time (hrs)	Lameness at Walk	Lameness at Trot	Pain on Palpation
0	0.828	0.966	0.351
24	<0.001	0.003	0.004
48	<0.001	<0.001	<0.001
72	<0.001	<0.001	<0.001
144	<0.001	<0.001	0.026

One DERAMAXX tablet-treated dog was treated with medetomidine for dysphoria during anesthetic recovery. The reversal agent, atipamezole, was then administered, and the dog recovered uneventfully. Twenty-two placebo and 14 DERAMAXX tablet-treated dogs received postoperative butorphanol injections. Two placebo-treated dogs and 1 DERAMAXX tablet-treated dog required additional analgesia in excess of the single butorphanol injection (treatment failures).

Four DERAMAXX tablet- and 5 placebo-treated dogs were withdrawn from the study due to adverse events including vomiting, diarrhea, and insufficient analgesia. There were no statistically significant changes in the mean values for hepatic or renal clinical pathology indices between DERAMAXX tablet- and placebo-treated dogs. Four DERAMAXX tablet- and 2 placebo-treated dogs with normal pretreatment values exhibited elevated postoperative serum bilirubin values. Three DERAMAXX tablet- and one placebo-treated dog with normal pretreatment values exhibited elevated postoperative ALT (alanine transferase) values. One DERAMAXX tablet-treated dog with a postoperative elevation in serum ALT, BUN, and total bilirubin values also vomited. None of the changes in clinical pathology values were considered clinically significant.

e. Statistical analysis: A Cochran-Mantel-Haenszel test statistic was calculated for the clinical evaluation variables of lameness at a walk, lameness at a trot, and pain on palpation. Modified ridit scores were used to represent the ordinal nature of the categories, and "site" was a stratification variable. A separate analysis was conducted to compare the test article and the placebo groups at each evaluation period.

   A generalized linear model assuming a binomial distribution and logit link function for the use (yes, no) of concomitant analgesic treatment was used. The concomitant analgesic treatment was defined as use within 24 hours post-surgery.

f. Conclusions: The results of this clinical study indicate that DERAMAXX™ Chewable Tablets, when administered orally at 3-4 mg/kg once daily for 7 days, are safe and effective for the control of orthopedic postoperative pain and inflammation. Statistically significant differences ($p<0.05$) at all postoperative evaluations for lameness, and pain on palpation demonstrate that DERAMAXX™ Chewable Tablets are effective for control of postoperative pain and inflammation in dogs following cranial cruciate surgery.

g. Adverse Reactions: Vomiting and diarrhea were the most common adverse events seen in both the DERAMAXX tablets- and placebo-treated groups.

Abnormal Health Findings in the Postoperative Orthopedic Pain Field Study*		
Clinical Observation	**DERAMAXX tablets N = 105**	**Placebo N = 102**
Vomiting	11	6
Diarrhea	6	7
Hematochezia	4	0
Melena	0	1
Anorexia	0	4
Incision site lesion (drainage, oozing)	11	6
Non-incision Skin Lesions (moist dermatitis, pyoderma)	2	0
Otitis Externa	2	0
Positive joint culture	1	0
Phlebitis	1	0
Hematuria	2	0
Conjunctivitis	1	2
Splenomegaly	1	0
Hepatomegaly	1	0
Death	0	1

*Dogs may have experienced more than one observation during the study. This table does not include one dog dosed at 16.92 mg/kg/day for the study duration. On the last day of treatment, this dog experienced vomiting, diarrhea, increased water intake and decreased appetite. Hematology and clinical chemistry values were unremarkable. The dog recovered uneventfully within 3 days of cessation of dosing.

2. Palatability Study

   a. Type of Study: Field Study

   b. Investigators:

Dr. Ben Jones Friendly Animal Clinic 2712 College Rd. Greensboro, NC 27408	Dr. Kristen Greeson Animal Clinic of Friendly Center 704-C Pembroke Rd. Greensboro, NC 27408
Dr. Janet Raczkowski Adams Farm Animal Hospital 5502 Adams Farm Lane Greensboro, NC 27407	Dr. Ronald Komich Greensboro Veterinary Hospital Inc. 3471 High Point Rd. Greensboro, NC 27406
Dr. Harvey Goho Total Care Veterinary Hospital 633 Greensboro Rd. High Point, NC 27260	

c. General Design: The study included one hundred (100) client-owned dogs. Dogs were dispensed two doses of DERAMAXX tablets and 1 dose of a palatable commercial vitamin product. Owners randomly dosed their dogs with one tablet daily on 3 consecutive days, and recorded their dogs' willingness to ingest the tablets from the hand, when placed in the food, or placed in the dog's mouth for 60 seconds.

d. Results: A total of 94% of dogs accepted the first dose of DERAMAXX tablets and 92% accepted the second dose.

e. Conclusions: DERAMAXX tablets are palatable to dogs.

III. Target Animal Safety

A. Two-Week Pharmacokinetics and Toxicity Study of Deracoxib in Dogs

1. Type of Study: Laboratory Study

2. Investigator: Randall P. Reed, BA
GD Searle & Co.
Skokie, Illinois

3. General design:

a. Purpose:

i) To determine the absorption of micronized deracoxib and the relationship of plasma concentrations of the test article with dosage and duration of dosing

ii) To assess the toxic effects of repeated dosing with the micronized test article

b. Test animals: Twelve Beagle dogs (male and female, 9-15 months of age, 8-14 kg body weight), were randomly assigned to four dosage groups (3 dogs/group).

c. Control: None

d. Dose form: Gelatin capsules filled with deracoxib

e. Route of administration: Orally to fasted dogs

f. Dosage: Table 2 lists the dose groups and duration of treatment

Table 2. Dose Groups for Deracoxib Tolerability Study

Group	Dosage (mg/kg/day)	No. Animals /Group	No. Days Treated
1	10	3	14
2	25	3	11
3	50	3	11
4	100	3	10

g. Test duration: Fourteen days

h. Parameters measured: general health, clinical observations, body weights, and necropsy, including gross and histopathology evaluations. Venous blood samples were collected at specified times post-dosing to measure plasma concentrations of deracoxib.

4. Results:

All dogs survived to the end of the study. Pharmacokinetic data collected in the study indicates that nonlinear elimination occurs with deracoxib at doses $\geq$ 10 mg/kg/day. Plasma levels of deracoxib may increase in a greater than dose proportional fashion at these doses.

There were no treatment related clinical observations in the 10 mg/kg group. Test article-related clinical observations at doses $\geq$ 25 mg/kg included vomiting and melena. In general, vomiting was observed sporadically in all animals in these dose groups. Melena was observed in most animals in the 25, 50, and 100 mg/kg treatment groups on Days 8 through 10. The incidence of melena in these groups appeared to be dose-related.

The body weights of dogs in the 25 and 50 mg/kg treatment groups were similar to pre-treatment values throughout the treatment period. By Day 8, one dog in the 50 mg/kg group and all three dogs in the 100 mg group exhibited slight weight losses that were likely associated with the administration of the test article.

Test-article related macroscopic findings in dogs given 10 mg/kg/day included moderate diffuse congestion of gut associated lymphoid tissues (GALT) in one dog and erosions/ulcers in the jejunum of another. Microscopic evaluation revealed erosions or ulcers in the jejunum and ileum of 2 dogs in the 10 mg/kg dose group.

Test-article related macroscopic findings at doses ≥ 25 mg/kg included small intestinal erosions/ulcers in one dog each from the 25 and 50 mg/kg treatment groups. At 100 mg/kg all dogs exhibited gastric ulcers and erosions/ulcerations of the small intestines. Evidence of intestinal hemorrhage in the dogs correlated with clinical observations of melena. There were no hepatic or renal lesions reported.

5. Conclusions:

Nonlinear elimination of deracoxib occurs at doses of 10 mg/kg and above. Elevated doses (≥ 25 mg/kg) are associated with COX-1 inhibition as evidenced by gastrointestinal signs.

The no effect dose level for micronized deracoxib administered once daily in gelatin capsules is less than 10 mg/kg. The frequency and severity of the gastrointestinal lesions increased with escalating doses. The gastrointestinal lesions reported in deracoxib-treated dogs at exaggerated doses are consistent with known non-steroidal anti-inflammatory drug (NSAID) induced adverse events.

B. 21-Day Safety Study in Dogs

1. Type of Study: Laboratory Study

2. Investigator: Ed Goldenthal PhD ATS
MPI Research Inc.
Mattawan, MI 49071-9399

3. General Design:

a. Purpose: To evaluate the safety of deracoxib in dogs

b. Test animals: Forty Beagle dogs (20 male and 20 female, 4-6 months of age, 6-9 kg body weight); four dogs per sex per treatment

c. Control: placebo tablets

d. Dose formulation: DERAMAXX tablets (final market tablet formulation)

e. Route of administration: Oral dosing within 30 minutes of feeding

f. Dosage used: 0, 4, 6, 8, 10 mg/kg body weight/day

g. Test duration: Twenty-one days

h. Parameters measured: clinical observations, food and water consumption, body weights, physical examinations, ophthalmic evaluations, hematology, clinical chemistry, urinalysis, buccal mucosal bleeding time, organ weights and anatomical pathology (macroscopic and microscopic)

4. Results:

All dogs survived to study termination. No adverse drug events were reported. There were no abnormal findings reported for clinical observations, food and water consumption, body weights, physical examinations, ophthalmic evaluations, organ weights, macroscopic pathologic examination, hematology, urinalysis or buccal mucosal bleeding time.

Clinical chemistry results showed a statistically significant ($p < 0.0009$) dose-dependent trend toward increased individual levels of blood urea nitrogen (BUN). Mean BUN values remained within the reference range at the labelled dose. No effects on other clinical chemistry values associated with renal function were reported. Renal histopathology revealed trace amounts of tubular degeneration/regeneration in all dose groups including placebo.

5. Conclusions:

DERAMAXX™ Chewable Tablets administered to healthy dogs within 30 minutes of feeding did not produce toxicity at doses $\leq$ 8 mg/kg once daily for 21 days. There was a dose-related increase in BUN values associated with administration of deracoxib tablets at all doses. No clear dose or test article relationship could be determined for the histopathologic changes noted.

C. 13-Week Capsule Study in Dogs with a 4-week Recovery Period

1. Type of Study: Laboratory (GLP) Study

2. Investigator: Dan W. Dalgard, DVM
Corning Hazelton, Inc.
Vienna, VA 22182

3. General Design:

a. Purpose:

i) To evaluate the subchronic toxicity of deracoxib when administered to dogs

ii) To evaluate the reversibility of any toxic effects following a 4-week recovery period

iii) To determine absorption of the test article and the relationship of plasma concentration with dosage and duration of dosing

b. Test animals: Forty-eight Beagle dogs (male and female, 4-6 months of age, 5-10 kg body weight) There were 4 dogs per sex per treatment group in the toxicity portion of the study. Additional animals were added to the control and high-dose groups for recovery groups (4 dogs/sex/dose). The pharmacokinetic section of the study used 3 dogs/sex/dose.

c. Control: Gelatin capsules

d. Dose formulation: Gelatin capsules filled with deracoxib

e. Route of administration: Oral

f. Dosage used: 0, 2, 4, and 8 mg/kg body weight/day

g. Test duration: Thirteen weeks

h. Parameters measured: clinical observations, food consumption, body weights, physical examinations, ophthalmoscopic and electrocardiograph evaluations, hematology, coagulation, clinical chemistry, urinalysis, organ weights and anatomical pathology (macroscopic and microscopic) Venous blood samples were

collected at specified times post-dosing to measure plasma concentrations of deracoxib.

4. Results:

All but one dog was in good health and survived to study termination. One high-dose (8 mg/kg) male dog died from bacterial septicemia associated with a renal abscess.

Analysis of plasma levels of deracoxib indicated that the drug was absorbed and systemically available at all doses throughout the study. Plasma concentrations increased with dose and were approximately proportional to dose over the dose range studied.

No test-article related changes were identified in clinical observations, physical examinations, or any of the other parameters measured.

5. Conclusions:

Deracoxib administered in capsules once daily for a period of 13 weeks, at doses up to 8 mg/kg body weight, did not produce toxicity in healthy dogs. The relationship between deracoxib administration and a renal abscess in one dog given 8 mg/kg is not clear.

IV. 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 medication out of reach of children. Consult a physician in case of accidental ingestion by humans. For use in dogs only."

V. Agency Conclusions

The data submitted in support of this NADA satisfy the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that DERAMAXX™ (deracoxib) Chewable Tablets for dogs, when used under labeled conditions of use are safe and effective for postoperative pain and inflammation associated with orthopedic surgery.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is needed to diagnose and provide guidance in the control of orthopedic postoperative pain. Furthermore, the veterinarian monitors patients for possible adverse effects of the drug.

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.

DERAMAXX™ Chewable Tablets are under the following U.S. patent numbers:

U.S. Patent Number	Date of Expiration
5,521,207	November 30, 2013

VI. Attachments:

Facsimile Labeling is attached as indicated below:

1. Package insert
2. Client Information Sheet
3. Bottle Labels