Approval Date: February 11, 2003

FREEDOM OF INFORMATION SUMMARY

Supplemental NADA 141-203

DERAMAXX™ Chewable Tablets
(deracoxib)

An additional claim for Chewable Tablets:
"… for the control of pain and inflammation associated with osteoarthritis in dogs at 1-2 mg/kg/day (0.45-0.91mg/lb/day) as a single daily dose, as needed."

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

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FREEDOM OF INFORMATION SUMMARY

1. General Information

a. File Number:	NADA 141-203
b. Sponsor:	Novartis Animal Health US, Inc 3200 Northline Avenue Suite 300 Greensboro, North Carolina 27408
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) – U.S. 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 daily dose of DERAMAXX tablets for the control of pain and inflammation associated with osteoarthritis in dogs is 1-2 mg/kg/day (0.45-0.91 mg/lb/day) as a single daily dose, as needed. The dose for postoperative orthopedic pain is 3-4 mg/kg/day (1.4 – 1.8 mg/lb/day) as a single daily dose, as needed, not to exceed 7 days of administration. 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 pain and inflammation associated with osteoarthritis, and for the control of postoperative pain and inflammation associated with orthopedic surgery in dogs $\geq$ 4 lbs (1.8 kg).

n. Effect of Supplement: The supplement to NADA 141-203 provides revisions to 21 CFR 520.538.
Indications for Use. To add a claim for the control of pain and inflammation associated with osteoarthritis in dogs.
Amount: To add a new dose range of 1-2 mg/kg (0.45-0.91 mg/lb).

2. Effectiveness

a. Dosage Characterization:

A urate crystal synovitis pain model in mixed breed dogs was utilized to evaluate an effective dose of deracoxib for the control of pain and inflammation associated with osteoarthritis. Doses of 0 (empty capsules), 0.3, 1, 3, and 10 mg/kg deracoxib (micronized solid in gelatin capsule) were administered 30 minutes prior to inducing synovitis via a parapatellar urate crystal injection. Pain, lameness and joint effusion assessments were made for each dog in all 5 groups. These evaluations included a clinical assessment for pain and lameness and force plate evaluation (measure of maximum weight bearing).

A baseline assessment was made prior to dosing and at 6 assessment times after the urate crystal injection. Dogs dosed at 1, 3, and 10 mg/kg of deracoxib showed greater improvement in pain, lameness, and force plate evaluations compared to placebo. Based on force plate measurements, and pain and lameness evaluations, a dose of 1-2 mg/kg body weight was chosen.

Summary Conclusion: Deracoxib was effective in controlling the pain and inflammation associated with induced synovitis in a dose-dependent manner. The results support the effectiveness of deracoxib at a once daily dose of 1-2 mg/kg for the control of pain and inflammation associated with osteoarthritis.

b. Substantial Evidence:

(1) Field Study

(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	Spencer Johnston, VMD, MS, Dipl. ACVS Department of Small Animal Clinical Sciences VMRCVM Blacksburg, VA 24061
Brian S. Beale, DVM, Dipl. ACVS Gulf Coast Veterinary Specialists 1111 West Loop South, Suite 160 Houston, TX 77027	Steven Martinez, DVM, MS, Dipl. ACVS College of Veterinary Medicine Washington State University Pullman, WA 99164
Darryl L. Millis, DVM, MS, Dipl. ACVS College of Veterinary Medicine University of Tennessee Knoxville, TN 37996-4500	Alan Cross, DVM, Dipl. ACVS University of Florida College of Veterinary Medicine Gainesville, FL 32610
	Walter C. Renberg, DVM, MS, Dipl. ACVS College of Veterinary Medicine Kansas State University Manhattan, KS 66506

(c) General Design:

1 Purpose: The objective of the study was to evaluate the effectiveness and safety of DERAMAXX tablets at a dose of 1-2 mg/kg (0.45 – 0.91 mg/lb) administered once daily for 43 days, for the control of pain and inflammation associated with osteoarthritis in dogs.

2 Test animals: Two hundred and nine client-owned dogs with clinical and radiographic signs of osteoarthritis were enrolled in the study. Male and female dogs from 7 locations, ranging from 1-14 years of age, and representing 41 different breeds were included in the study. A total of 105 dogs were treated with DERAMAXX tablets and 104 received the placebo.

3 Control: The placebo was identical to DERAMAXX™ Chewable Tablets without the active ingredient.

4 Dosage form: DERAMAXX™ Chewable Tablets (final market formulation)

5 Route of administration: oral

6 Dosage used: 1-2 mg/kg (0.45 – 0.91 mg/lb) administered once daily

7 Test duration: 43 days

8 Parameters measured: Seven days pre-study, and on Days 0, 14, 28, and 42, the investigators assessed each animal for lameness at a walk, lameness at a trot, pain response to palpation, and willingness to bear weight on the affected limb. Ground reaction forces were evaluated by force plate measurements (peak vertical force and vertical impulse area). Additionally, owners evaluated response to treatment based on their perception of the pet's quality of life, lameness, and level of activity at Days 14, 28, and 42.

Prior to the study and again on Day 42, hematology, clinical chemistry samples, and buccal bleeding times were evaluated.

(d) Results: A total of 194 dogs were included in the clinical pathology evaluations, 114 dogs contributed force plate data, and a total of 181 dogs were included in the effectiveness evaluation. The most common radiographically represented arthritic joints were stifle, hip and elbow. There was no statistically significant difference in buccal bleeding times between DERAMAXX- and placebo-treated dogs. All values remained within normal limits [< 5 minutes][1]. For the parameters measured in (viii) above, the following variables showed statistically significant ($p<0.05$) differences in favor of DERAMAXX tablets, for most or all time periods: vertical impulse area, peak vertical force, owner evaluation of quality of life, lameness and level of activity. There was no statistically significant difference between DERAMAXX tablets and placebo cases for the veterinarian clinical evaluations at any of the time points. Results are presented in Tables 1-5 below.

Table 1: Summary Statistics and p-values for Vertical Impulse Area over All Sites.

Treatment	Day	N	Mean	SD	Minimum	Maximum	p-value[a]
DERAMAXX	0	56	9.43	2.61	4.36	18.28	
	14	52	9.78	2.63	4.89	18.10	
	28	53	9.81	2.69	4.78	19.01	
	42	54	9.89	2.59	5.36	18.66	0.0013
Placebo	0	58	9.76	3.16	5.54	19.17	
	14	57	9.69	3.32	5.09	20.08	
	28	57	9.69	3.28	5.21	19.80	
	42	58	9.74	3.41	5.17	20.72	

[a] = Significant difference in favor of DERAMAXX compared to placebo for the entire post-treatment period. The Day 0 (pre-treatment value of each subject) was used as a covariate.

[1] Duncan JR, Prasse KW, 1997, Veterinary Laboratory Medicine, 2nd edition.

Table 2: Summary Statistics and p-values for Peak Vertical Force over All Sites.

Treatment	Day	N	Mean	SD	Minimum	Maximum	p-value[a]
DERAMAXX	0	56	59.69	15.93	25.85	111.60	
	14	52	62.66	14.83	31.67	106.10	
	28	53	63.13	14.87	32.06	109.30	
	42	54	64.13	14.28	39.53	111.80	0.0004
Placebo	0	58	66.40	18.21	33.99	112.80	
	14	57	65.92	18.82	31.28	110.60	
	28	57	66.01	18.54	30.82	118.70	
	42	58	66.36	19.32	38.55	112.50	

[a] = Significant difference in favor of DERAMAXX compared to placebo for the entire post-treatment period. The Day 0 (pre-treatment value of each subject) was used as a covariate.

Table 3: Percentage of Owners Rating Improvement in Dog's Quality of Life

	Number of animals rated as "improved" by owners compared with Day 0 / Total number of animals rated by owners	
Day	DERAMAXX	Placebo
Day 14	50/91* (54.9%)	32/90 (35.6%)
Day 28	53/88* (60.2%)	35/88 (39.8%)
Day 42	58/89* (65.2%)	35/87 (40.2%)
* Statistical significance compared with the placebo group at $p<0.05$		

Table 4: Percentage of Owners Rating Improvement in Dog's Lameness

	Number of animals rated as "improved" by owners compared with Day 0 / Total number of animals rated by owners	
Day	DERAMAXX	Placebo
Day 14	37/91 (40.7%)	31/89 (34.8%)
Day 28	51/88* (58.0%)	30/88 (34.1%)
Day 42	54/89* (60.7%)	34/87 (39.1%)
* Statistical significance compared with the placebo group at $p<0.05$		

Table 5: Percentage of Owners Rating Improvement in Dog's Overall Level of Activity

	Number of animals rated as "improved" by owners compared with Day 0 / Total number of animals rated by owners	
Day	DERAMAXX	Placebo
Day 14	44/91 (48.4%)	32/89 (36.0%)
Day 28	50/88* (56.8%)	30/88 (34.1%)
Day 42	58/89* (65.2%)	33/87 (37.9%)
* Statistical significance compared with the placebo group at $p<0.05$		

There was a statistically significant elevation (p-value = 0.0463) of BUN (blood urea nitrogen) on Day 42 between DERAMAXX and the placebo groups (the p-value is adjusted for the mean pre-treatment BUN value for each group). The mean BUN at Day 42 for DERAMAXX was 20.14 mg/dl and the mean value was 16.94 mg/dl for the placebo group (normal range 6-25 mg/dl for the study laboratory). The ALT (alanine transferase) values for 5 DERAMAXX and 1 placebo cases were normal pre-study and elevated at the end of the study. The mean increase in ALT for the 5 DERAMAXX and 1 placebo cases were 69.4 U/L and 58.0 U/L, respectively. The AST (aspartate transferase) values for 3 DERAMAXX and zero placebo cases were normal pre-study and elevated post-study. The mean increase in AST for the DERAMAXX cases was 76.0 U/L. The potassium values for 4 DERAMAXX and 1 placebo case were normal pre-study and elevated post-study. The mean increase in potassium for the 4 DERAMAXX and 1 placebo cases was 0.5 mEq/L, for both. The phosphorous values (non-hemolyzed samples) for 7 DERAMAXX and 2 placebo cases were normal pre-study and elevated post-study. The mean increase for phosphorous in both groups was 0.5 mg/dl. These changes in clinical pathology values were not considered clinically significant.

(e) Statistical analysis: The force plate variables were evaluated by a repeated measures analysis of covariance. Clinical and owner-assessed variables were evaluated by generalized estimating equations. The owner's assessments were classified as either "Improved" or "No change/Became worse", and this score was evaluated with a Cochran-Mantel-Haenszel test.

(f) Conclusions: Statistically significant differences ($p \leq 0.05$) at most evaluation points for vertical impulse area, peak vertical force, and owners' evaluations demonstrated the effectiveness of DERAMAXX™ Chewable Tablets for this claim. The results of this study indicate that DERAMAXX™ Chewable Tablets, when administered at 1-2 mg/kg (0.45-0.91 mg/lb) orally once daily, as needed, are safe and effective for the control of pain and inflammation associated with osteoarthritis.

(g) Adverse Reactions: Adverse events occurred during the study in both the placebo and DERAMAXX-treated dogs. Vomiting and diarrhea were the most common adverse events seen in both the DERAMAXX tablets- and placebo-treated groups.

Abnormal Health Findings in the Osteoarthritis Field Study[1]		
Clinical Observation	**DERAMAXX n=105**	**Placebo n=104**
Vomiting	3	4
Diarrhea/Soft Stool	3	2
Weight Loss	1	0
Abdominal Pain (splinting)	0	1
Seizure	1	0
Lethargy	0	1
Pyoderma/Dermatitis	2	0
Unilateral Conjunctivitis	1	0
Scleral Injection	0	1
Hematuria/UTI	1	0
Splenomegaly*	1	0
Grade II Murmur Systolic	1	0

[1] Dogs may have experienced more than one of the observations during the study.

*This dog was less active and eating less on enrollment, with elevated WBC, amylase, and AST, and died 1 month after exiting the study. The dog was withdrawn from the study on Day 17 with anorexia, lethargy and a suspicion of diarrhea. Follow-up laboratory analyses revealed hypoalbuminemia, hyperphosphatemia, elevated AST and decreased BUN. Follow-up treatment included other anti-inflammatories and antibiotics.

3. Target Animal Safety

a. For information about tolerance and short-term toxicity studies conducted to demonstrate the safety of deracoxib in dogs, please refer to the Freedom of Information summary dated August 21, 2002, (NADA 141-203).

b. A 6-Month Target Animal Safety Study in Dogs with DERAMAXX™ Chewable Tablets.

(1) Type of Study: Safety Study (GLP)

(2) Investigator: Ed Goldenthal, Ph.D., ATS
MPI Laboratory, Inc.
Mattawan, MI 49071

(3) General design:

(a) Purpose: The study was conducted to evaluate the safety of DERAMAXX™ Chewable Tablets administered orally on a daily basis for 6 months.

(b) Test animals: Sixty healthy Beagle dogs (30 male, 30 female, approximately 4 months of age), five per sex per treatment.

(c) Control: The placebo was identical to DERAMAXX™ Chewable Tablets without the active ingredient.

(d) Dose form: DERAMAXX™ Chewable Tablets (final market formulation).

(e) Route of administration: oral

(f) Dosages used:

Table 6. Treatment Groups for 6 month Safety Study

Tx Group	Dose mg/kg	Number and Sex of Animals
1	Placebo	5 males, 5 females
2	2 mg/kg/day (1X)	5 males, 5 females
3	4 mg/kg/day (2X)	5 males, 5 females
4	6 mg/kg/day (3X)	5 males, 5 females
5	8 mg/kg/day (4X)	5 males, 5 females
6	10 mg/kg/day (5X)	5 males, 5 females

(g) Test duration: Twenty-six weeks

(h) Parameters measured: Clinical observations, food consumption, body weights, physical examinations, ophthalmoscopic evaluations, buccal mucosal bleeding time, hematology including bone marrow smear evaluation, clinical chemistry, urinalysis, organ weights and anatomical pathology (histologic and gross). Dosing was confirmed via assay for deracoxib of a single plasma sample from each dog.

(4) Results: All dogs survived to termination of the study.

(a) There were no abnormal feces, and no abnormal findings on clinical observations, food and water consumption, body weights, physical examinations, ophthalmoscopic evaluations, gross pathology examinations, bone marrow smears, hematology, or buccal mucosal bleeding time.

(b) Urinalysis results showed hyposthenuria (specific gravity ≤ 1.005) and polyuria in one male and one female in the 6 mg/kg group after 6 months of treatment.

(c) After 6 months of treatment, the mean BUN (blood urea nitrogen) values increased for dogs in the 6, 8, and 10 mg/kg/day treatment groups. These values were 30, 35.3, and 48.2 mg/dl respectively. (Normal BUN reference range is 7-32 mg/dl.[2]) No effects were seen on any other clinical chemistry parameters, including other variables associated with renal physiology (serum creatinine, serum electrolytes, and urine sediment evaluation).

(d) Renal lesions were seen on histopathologic examination, but not on gross examination. Dose dependent focal renal tubular degeneration/regeneration was seen in some dogs dosed at 6, 8, and 10 mg/kg/day. Focal renal papillary necrosis was seen in 3 dogs dosed at 10 mg/kg/day and one dog dosed at 8 mg/kg/day. There was no evidence of gastrointestinal, hepatic or hematopoetic pathology in any of the dogs.

(e) Evaluation of the pharmacokinetic data demonstrated that dose proportional increases in systemic drug exposure were achieved. No significant gender or dose-by-gender interactions were observed.

(5) Conclusions: DERAMAXX tablets were clinically well tolerated by dogs when administered at doses up to 10 mg/kg/day for 26 weeks even though, there was a dose-dependent increase in BUN values at doses ≥ 6 mg/kg/day. Focal renal tubular degeneration/regeneration was seen at doses ≥ 6 mg/kg/day.

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 supplemental 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."

5. Agency Conclusions

The data submitted in support of this supplemental 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, are safe and

[2] Willard, Tverten, Turnwald. Small Animal Clinical Diagnosis by Laboratory Methods. 2nd edition, 1994.

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

DERAMAXX™ Chewable Tablets are restricted to use by or on the order of a licensed veterinarian because professional expertise is needed to diagnose canine osteoarthritis and to monitor response to treatment.

Under Section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for three years of marketing exclusivity beginning on the date of the approval. The **three years** of marketing exclusivity applies only to the additional claim of control of pain and inflammation associated with osteoarthritis in dogs for which this supplement is approved.

In accordance with 21 CFR 514.106(b)(2)(v) this is a Category II supplemental application that did not require a reevaluation of safety or effectiveness data in the parent application.

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

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

6. Attachments:

Facsimile Labeling is attached as indicated below:

(a) Package insert

(b) Client Information Sheet

(c) Bottle Labels