

Approval Date: FEB 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

NADA 141-203

FOIS 1

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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:

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(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

§ 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	0.0013
	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	
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	0.0004
	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	
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

Day	Number of animals rated as "improved" by owners compared with Day 0 / Total number of animals rated by owners	
	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

Day	Number of animals rated as "improved" by owners compared with Day 0 / Total number of animals rated by owners	
	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

Day	Number of animals rated as "improved" by owners compared with Day 0 / Total number of animals rated by owners	
	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 Study¹		
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 hematopoietic 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>U.S. Patent Number</u>	<u>Date of Expiration</u>
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

Deramaxx™ (deracoxib)

Chewable Tablets

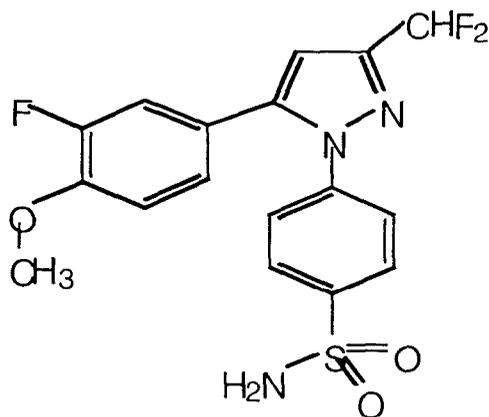
For Oral Use In Dogs Only

Caution:

U.S. Federal Law restricts the use of this product by or on the order of a licensed veterinarian.

Description:

DERAMAXX (deracoxib) tablets are a non-narcotic, non-steroidal anti-inflammatory drug of the coxib class. DERAMAXX tablets are round, biconvex, chewable tablets that contain deracoxib formulated with beefy flavoring. The molecular weight of deracoxib is 397.38. The empirical formula is C₁₇H₁₄F₃N₃O₃S. Deracoxib is 4-[5-(3-difluoro-4-methoxyphenyl)-(difluoromethyl)-1H-pyrazole-1-yl] benzenesulfonamide, and can be termed a diaryl substituted pyrazole. The structural formula is:



Clinical Pharmacology

Mode of Action:

DERAMAXX tablets are a member of the coxib class of non-narcotic, non-steroidal, cyclooxygenase-inhibiting anti-inflammatory drugs for the control of postoperative pain and inflammation associated with orthopedic surgery and for the control of pain and inflammation associated with osteoarthritis in dogs.

Data indicate that deracoxib inhibits the production of PGE₁ and 6-keto PGF₁ by its inhibitory effects on prostaglandin biosynthesis¹. Deracoxib inhibited COX-2 mediated PGE₂ production in LPS-stimulated human whole blood².

Cyclooxygenase-1 (COX-1) is the enzyme responsible for facilitating constitutive physiological processes (e.g., platelet aggregation, gastric mucosal protection, renal perfusion).³ Cyclooxygenase-2 (COX-2) is responsible for the synthesis of inflammatory mediators.⁴ Both COX isoforms are constitutively expressed in the canine kidney.⁵ At doses of 2-4 mg/kg/day, DERAMAXX tablets do not inhibit COX-1 based on *in vitro* studies using cloned canine cyclooxygenase⁶. The clinical relevance of this *in vitro* data has not been shown.

Although the plasma terminal elimination half-life for DERAMAXX tablets is approximately 3 hours, a longer duration of clinical effectiveness is observed.

Summary pharmacokinetics of DERAMAXX tablets are listed in Table 1

Table 1: Pharmacokinetics of Deracoxib

Parameter	Value
T _{max} ^a	2 hours
Oral Bioavailability (F) ^a	> 90% at 2 mg/kg
Terminal elimination half-life ^b	3 hours at 2-3 mg/kg 19 hours at 20 mg/kg
Systemic Clearance ^b	~ 5 ml/kg/min at 2 mg/kg ~1.7 ml/kg/min at 20 mg/kg
Volume of Distribution ^c	~ 1.5 L/kg
Protein binding ^d	> 90%

a Values obtained following a single 2.35 mg/kg dose

b Estimates following IV administration of deracoxib as an aqueous solution

c Based upon a dose of 2 mg/kg of deracoxib

d Based upon *in vitro* plasma concentrations of 0.1, 0.3, 1.0, 3.0, 10.0 µg/ml

Non-linear elimination kinetics are exhibited at doses above 8 mg/kg/day, at which competitive inhibition of constitutive COX-1 may occur.

Deracoxib is not excreted as parent drug in the urine. The major route of elimination of deracoxib is by hepatic biotransformation producing four major metabolites, two of which are characterized as products of oxidation and o-demethylation. The majority of deracoxib is excreted in feces as parent drug or metabolite.

Large intersubject variability was observed in drug metabolite profiles of urine and feces. No statistically significant differences between genders were observed.

Indications and Usage:

Osteoarthritis Pain and Inflammation:

DERAMAXX Chewable Tablets are indicated for the control of pain and inflammation associated with osteoarthritis in dogs.

Postoperative Orthopedic Pain and Inflammation:

DERAMAXX Chewable Tablets are indicated for the control of postoperative pain and inflammation associated with orthopedic surgery in dogs ≥ 4 lbs (1.8 kg).

Dosage and Administration:

Always provide Client Information Sheet with prescription.

Osteoarthritis Pain and Inflammation: The daily dose of DERAMAXX tablets for the control of pain and inflammation associated with osteoarthritis in dogs is 1 to 2 mg/kg/day (0.45 -0.91 mg/lb/day) as a single daily dose, as needed.

Postoperative Orthopedic Pain and Inflammation: The daily dose of DERAMAXX tablets for postoperative orthopedic pain is 3 to 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.

Since DERAMAXX tablet bioavailability is greatest when taken with food, postprandial administration is preferable. However, DERAMAXX tablets have been shown to be effective under both fed and fasted conditions; therefore, they may be administered in the fasted state if necessary. For postoperative orthopedic pain, administer DERAMAXX tablets prior to the procedure. Tablets are scored and dosage should be calculated in half-tablet increments. In clinical practice it is recommended to adjust the individual patient dose while continuing to monitor the dog's status until a minimum effective dose has been reached.

Contraindications:

Dogs with known hypersensitivity to deracoxib should not receive DERAMAXX tablets.

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 use in dogs only.**

All dogs should undergo a thorough history and physical examination before the initiation of NSAID therapy. Appropriate laboratory tests to establish hematological and serum biochemical baseline data prior to, and periodically during, administration of any NSAID is recommended.

For technical assistance or to report suspected adverse events, call 1-800-332-2761.

Precautions:

Plasma levels of deracoxib may increase in a greater than dose-proportional fashion above 8 mg/kg/day. DERAMAXX tablets have been safely used during field studies in conjunction with other common medications, including heartworm preventatives, anthelmintics, anesthetics, pre-anesthetic medications, and antibiotics. If additional pain medication is needed after a daily dose of DERAMAXX tablets, a non-NSAID class of analgesic may be necessary. It is not known whether dogs with a history of hypersensitivity to sulfonamide drugs will exhibit hypersensitivity to DERAMAXX tablets. The safe use of DERAMAXX tablets in dogs younger than 4 months of age, dogs used for breeding, or in pregnant or lactating dogs has not been evaluated.

As a class, cyclooxygenase inhibitory NSAIDs may be associated with gastrointestinal and renal toxicity. Sensitivity to drug-associated adverse events varies with the individual patient. Patients at greatest risk for renal toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be carefully approached. Appropriate monitoring procedures should be employed during all surgical procedures. NSAIDs may inhibit the prostaglandins, which maintain normal homeostatic function. Such anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease that has not been previously diagnosed. The use of parenteral fluids during surgery should be considered to decrease potential renal complications when

using NSAIDs perioperatively. Since many NSAIDs possess the potential to produce gastrointestinal ulceration, concomitant use of DERAMAXX tablets with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided or closely monitored. The use of concomitantly protein-bound drugs with DERAMAXX tablets has not been studied in dogs. Commonly used protein-bound drugs include cardiac, anticonvulsant and behavioral medications. The influence of concomitant drugs that may inhibit metabolism of DERAMAXX tablets has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy.

Animal Safety:

In a 6-month study, dogs were dosed with DERAMAXX at 0, 2, 4, 6, 8 and 10 mg/kg with food once daily for 6 consecutive months. There were no abnormal feces, and no abnormal findings on clinical observations, food and water consumption, body weights, physical examinations, ophthalmoscopic evaluations, macroscopic pathological examinations, hematology, or buccal bleeding time. 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. After 6 months of treatment, the mean BUN values for dogs treated with 6, 8, or 10 mg/kg/day were 30.0, 35.3, and 48.2 mg/dL respectively. 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). Dose dependent focal renal tubular degeneration/regeneration was seen in some dogs treated at 6, 8, and 10 mg/kg/day. Focal renal papillary necrosis was seen in 3 dogs dosed at 10 mg/kg/day and in one dog dosed at 8 mg/kg/day. No renal lesions were seen at the label doses of 2 and 4 mg/kg/day. There was no evidence of gastrointestinal, hepatic, or hematopoietic pathology at any of the doses tested.

In a laboratory study, healthy young dogs were dosed with deracoxib tablets once daily, within 30 minutes of feeding, at doses of 0, 4, 6, 8, and 10 mg/kg body weight for 21 consecutive days. 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 evaluation, hematology, urinalyses, or buccal mucosal bleeding time. In the clinical chemistry results there was a statistically significant ($p < 0.0009$) dose-dependent trend toward increased levels of blood urea nitrogen (BUN). Mean BUN values remained within historical normal limits at the label dose. No effects on other clinical chemistry values associated with renal function were reported. There was no evidence of renal, gastrointestinal, hepatic or biliary lesions noted during gross necropsy. Renal histopathology revealed trace amounts of tubular degeneration/regeneration in all dose groups including placebo, but no clear dose relationship could be determined. There was no histopathologic evidence of gastrointestinal, hepatic or biliary lesions.

In another study, micronized deracoxib in gelatin capsules

was administered once daily to healthy young dogs at doses of 10, 25, 50, and 100 mg/kg body weight for periods up to 14 consecutive days. Food was withheld prior to dosing. Non-linear elimination kinetics occurred at all doses. At doses of 25, 50, and 100 mg/kg, reduced body weight, vomiting, and melena occurred. Necropsy revealed gross gastrointestinal lesions in dogs from all dose groups. The frequency and severity of the lesions increased with escalating doses. At 10 mg/kg, moderate diffuse congestion of gut associated lymphoid tissues (GALT) and erosions/ulcers in the jejunum occurred. At 100 mg/kg, all dogs exhibited gastric ulcers and erosions/ulcerations of the small intestines. There were no hepatic or renal lesions reported at any dose in this study.

In a 13-week study, deracoxib in gelatin capsules was administered to healthy dogs at doses of 0, 2, 4, and 8 mg/kg/day. No test-article related changes were identified in clinical observations, physical exams, or any of the other parameters measured. One dog in the 8 mg/kg dose group died from bacterial septicemia secondary to a renal abscess. The relationship between deracoxib administration and the renal abscess is not clear.

Palatability:

DERAMAXX tablets were evaluated for palatability in 100 client-owned dogs of a variety of breeds and sizes. Dogs received two doses of DERAMAXX tablets, one on each of two consecutive days. DERAMAXX tablets were accepted by 94% of dogs on the first day of dosing and by 92% of dogs on the second day of dosing.

Effectiveness:

DERAMAXX tablets were evaluated in masked, placebo-controlled multi-site field studies involving client-owned animals to determine effectiveness.

Postoperative Orthopedic Pain and Inflammation Field Study:

In this study, 207 dogs admitted to veterinary hospitals for repair of a cranial cruciate injury were randomly administered DERAMAXX tablets or a placebo. Drug administration started the evening before surgery and continued once daily for 6 days postoperatively. Effectiveness was evaluated in 119 dogs and safety was evaluated in 207 dogs. Statistically significant differences in favor of DERAMAXX tablets were found for lameness at walk and trot, and pain on palpation values at all post-surgical time points. The results of this field study demonstrate that DERAMAXX tablets, when administered daily for 7 days are effective for the control of postoperative pain and inflammation associated with orthopedic surgery.

Adverse Reactions:

A total of 207 dogs of forty three (43) different breeds, 1-15 years old, weighing 7-141 lbs were included in the field safety analysis. The following table shows the number of dogs displaying each clinical observation.

Abnormal Health Findings in The Postoperative Orthopedic Pain Field Study¹		
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

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

This table does not include one dog that was dosed at 16.92 mg/kg/day for the study duration. Beginning 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.

Incisional drainage was most prevalent in dogs enrolled at a single study site. 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-treated dogs and two placebo-treated dogs exhibited elevated bilirubin during the dosing phase. One DERAMAXX tablet-treated dog exhibited elevated ALT, BUN and total bilirubin and a single vomiting event. None of the changes in clinical pathology values were considered clinically significant.

The results of this clinical study demonstrate that DERAMAXX tablets, when administered daily for 7 days to control postoperative orthopedic pain and inflammation in dogs, are well tolerated.

Osteoarthritis Pain and Inflammation Field Study:

Two hundred and nine (209) client-owned dogs with clinical and radiographic signs of osteoarthritis of at least one appendicular joint were enrolled in this study. A total of 194 dogs were included in the safety evaluation and a total of 181 dogs were included in the effectiveness evaluation. The effectiveness of DERAMAXX tablets in the control of pain and inflammation associated with osteoarthritis was demonstrated in a placebo-controlled, masked study

evaluating the anti-inflammatory and analgesic effects of DERAMAXX tablets. Tablets were administered by the owner at approximately 1-2 mg/kg/day for forty-three (43) consecutive days.

In general, statistically significant ($p \leq 0.05$) differences in favor of DERAMAXX were seen for force plate parameters (vertical impulse area, peak vertical force) and owner evaluations (quality of life, lameness and overall level of activity).

The results of this field study demonstrate that DERAMAXX tablets, when administered at 1-2 mg/kg/day for 43 days, are effective for the control of pain and inflammation associated with osteoarthritis.

Adverse Reactions:

DERAMAXX was well tolerated and the incidence of clinical adverse reactions was comparable in DERAMAXX and placebo-treated animals. A total of 209 dogs of 41 breeds, 1-14 years old, weighing 17-177 lbs were included in the field safety analysis. The following table shows the number of dogs displaying each clinical observation.

Abnormal Health Findings in the Osteoarthritis Field Study ¹		
Clinical Observation	DERAMAXX tablets 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.

Complete blood count, serum chemistry, and buccal bleeding time analysis were conducted at the beginning and end of the trial. Mean values of all CBC and chemistry results for both DERAMAXX and placebo-treated dogs were within normal limits. There was no statistically significant difference in the

buccal bleeding time between DERAMAXX and placebo-treated dogs before or after the study, and all results remained within normal limits (less than 5 minutes). The results of this field study demonstrate that DERAMAXX is safe and effective for the control of pain and inflammation associated with osteoarthritis in dogs.

During this trial, dogs were safely treated with a variety of commonly used medications, including antibiotics, anti-parasitocides, topical flea aduclitides and thyroid supplements.

The results of this field study demonstrate that DERAMAXX tablets are well tolerated when administered at 1-2 mg/kg/day for up to 43 days for the control of pain and inflammation associated with osteoarthritis.

Storage Conditions:

DERAMAXX tablets should be stored at room temperature between 59° and 86°F (15-30°C).

Keep this and all medications out of reach of children.

How Supplied:

DERAMAXX tablets are available as 25 mg and 100 mg round, brownish, half-scored tablets in 7, 30, and 90 count bottles.

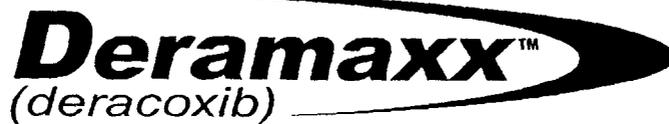
Manufactured by: G.D.Searle & Co.
Caguas, Puerto Rico

Manufactured for: Novartis Animal Health US, Inc.
Greensboro, NC 27408 USA

References:

1. Data on File
2. Data on File
3. Smith, et al.: "Pharmacological Analysis of Cyclo-oxygenase -1 in Inflammation," Proc. Natl. Acad. Sci. USA (October 1998) 95: 13313-13318, Pharmacology.
4. Zhang, et al.: "Inhibition of Cyclo-oxygenase-2 Rapidly Reverses Inflammatory Hyperalgesia and Prostaglandin E2 Production," *JPET*, (1997) 283: 1069-1075.
5. Verburg, KM et al. "Cox-2 Specific Inhibitors: Definition of a New Therapeutic Concept." *Amer J of Therapeutics* 8, 49-64, 2001.
6. Data on File
NADA # 141-203, Approved by FDA
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NAH/DXB-T/VI/2
11/02



DERAMAXX™ Chewable Tablets: Information for Dog Owners

DERAMAXX Chewable Tablets are for the control of pain and inflammation due to osteoarthritis or following orthopedic surgery.

This summary contains important information about DERAMAXX tablets. You should read this information before starting your dog on DERAMAXX tablets. This sheet is provided only as a summary and does not take the place of instructions from your veterinarian. Talk to your veterinarian if you do not understand any of this information or you want to know more about DERAMAXX tablets.

What is DERAMAXX?

DERAMAXX tablets are a prescription non-steroidal anti-inflammatory drug (NSAID) of the coxib class. They are indicated for the control of postoperative pain and inflammation associated with orthopedic (bone) surgery in dogs and for the control of pain and inflammation (soreness) associated with osteoarthritis in dogs. The tablets are flavored to make administration more convenient.

What kind of results can I expect when my dog takes DERAMAXX tablets for postoperative orthopedic pain and inflammation?

DERAMAXX tablets allow your dog to recover more comfortably by controlling pain and inflammation that follow orthopedic surgery.

- Control of pain and inflammation may vary from dog to dog.
- If DERAMAXX tablets are not given according to your veterinarian's directions, your dog's pain may return.
- Consult your veterinarian if your dog appears to be uncomfortable.

What kind of results can I expect when my dog takes DERAMAXX tablets for pain and inflammation due to osteoarthritis?

Osteoarthritis is a painful condition caused by damage to cartilage and other parts of the joint that may result in the following changes or signs in your dog:

- Limping or lameness
- Decreased activity or exercise (reluctance to stand, climb stairs, jump or run, or difficulty in performing these activities)
- Stiffness or decreased movement of joints

While DERAMAXX is not a cure for osteoarthritis, it can control the pain and inflammation of osteoarthritis and improve your dog's mobility. Response may vary from dog to dog but can be quite dramatic.

- If DERAMAXX is discontinued or is not given as directed, your dog's pain and inflammation may come back.

What dogs should not take DERAMAXX tablets?

Your dog should not be given DERAMAXX tablets if s/he:

- Has had an allergic reaction to deracoxib, the active ingredient in DERAMAXX tablets
- Has had an allergic reaction (such as hives, facial swelling, or red or itchy skin) to aspirin or other NSAIDs
- Is presently taking aspirin, other NSAIDs, or corticosteroids (unless directed by your veterinarian).

DERAMAXX tablets should only be given to dogs.

People should not take DERAMAXX tablets. Keep DERAMAXX tablets and all medication out of reach of children. Call your physician immediately if you accidentally take DERAMAXX tablets.

What to discuss with your veterinarian before giving DERAMAXX tablets?

Tell your veterinarian about:

- Any side effects your dog has experienced from DERAMAXX tablets or other NSAIDs
- Any digestive upset (vomiting or diarrhea) your dog has had
- Any kidney disease your dog has had
- Any other medical problems or allergies that your dog has now or has had in the past
- All medications that you are giving your dog or plan to give your dog, including those you can get without prescription and any dietary supplements
- If you plan to breed your dog, or if your dog is pregnant or nursing

Talk to your veterinarian about

- The orthopedic surgery your dog will undergo
- What tests might be done before surgery is performed or DERAMAXX tablets are prescribed

- The signs of pain or inflammation that may occur after surgery
- Normal events that can be expected after your dog undergoes surgery
- The proper amount of exercise after surgery to aid recovery
- The signs of osteoarthritis you have observed (for example, limping or stiffness)
- The importance of weight control, physical therapy and exercise in the management of osteoarthritis
- How often your dog may need to be examined by your veterinarian
- The risks and benefits of using DERAMAXX tablets

How to give DERAMAXX tablets to your dog.

DERAMAXX tablets should be given according to your veterinarian's instructions. Your veterinarian will tell you what amount of DERAMAXX tablets is right for your dog and for how long they should be given. Do not change the way you give DERAMAXX tablets to your dog without first speaking with your veterinarian. DERAMAXX tablets should be given by mouth and may be given with or without food, although with food is preferable.

What are the possible side effects that may occur in my dog during therapy with DERAMAXX tablets?

DERAMAXX tablets, like all other drugs, may cause some side effects in individual dogs. Serious but rare side effects have been reported in dogs taking non-steroidal anti-inflammatory drugs (NSAIDs). It is important to stop the medication and contact your veterinarian immediately if you think your dog may have a medical problem or side effect while on DERAMAXX tablets. If you have additional questions about possible side effects, talk with your veterinarian or call 1-800-332-2761.

Look for the following side effects that may indicate that your dog is having a problem with DERAMAXX tablets or may have another medical problem:

- Vomiting
- Change in bowel movements such as diarrhea or change in stool color
- Change in drinking or urination
- Decrease in appetite

Can DERAMAXX tablets be given with other medications?

DERAMAXX tablets should not be given with other non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids (for example, aspirin, carprofen, etodolac, prednisone), unless directed by your veterinarian.

Tell your veterinarian about all medications that you have given your dog in the past, and any medications that you are planning to give with DERAMAXX tablets. This should include any medications that you can get without a prescription and any dietary supplements. Your veterinarian may want to evaluate the potential for any drug interactions and to assure drug compatibility.

What can I do in case my dog eats more than the prescribed amount of DERAMAXX tablets?

Contact your veterinarian immediately if your dog eats more than the prescribed amount of DERAMAXX tablets.

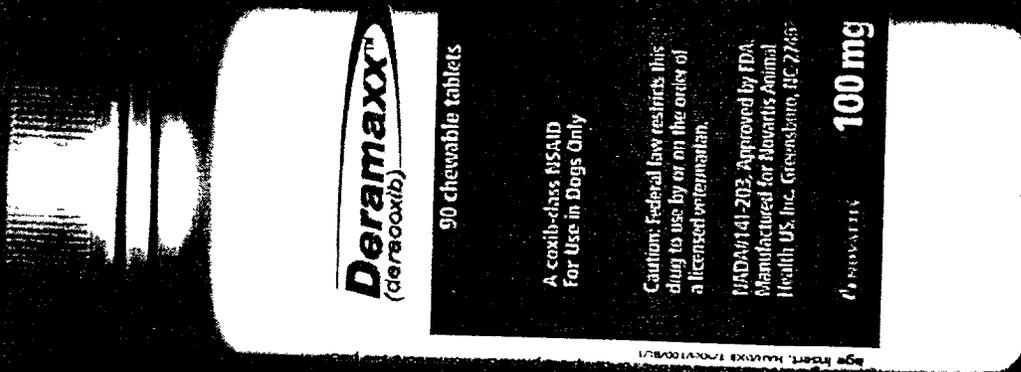
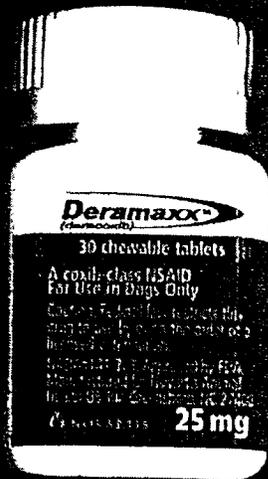
What else should I know about DERAMAXX tablets?

This sheet provides a summary of information about DERAMAXX tablets. If you have any questions or concerns about DERAMAXX tablets, postoperative orthopedic pain and inflammation, or osteoarthritis, talk to your veterinarian.

As with all prescribed medications, DERAMAXX tablets should only be given to the dog for which they are prescribed. They should be given to your dog only for the condition for which they were prescribed, at the prescribed dose, as directed by your veterinarian. It is important to periodically discuss your dog's response to DERAMAXX tablets at regular checkups. Your veterinarian will best determine if your dog is responding as expected and if your dog should continue receiving DERAMAXX tablets.

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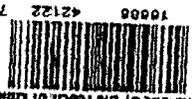
NAH/DXB-T/CI/2
10/02



Storage Conditions: Store at room temperature between 59° and 86°F (15-30°C).
WARNING: Keep this and all medications out of the reach of children.



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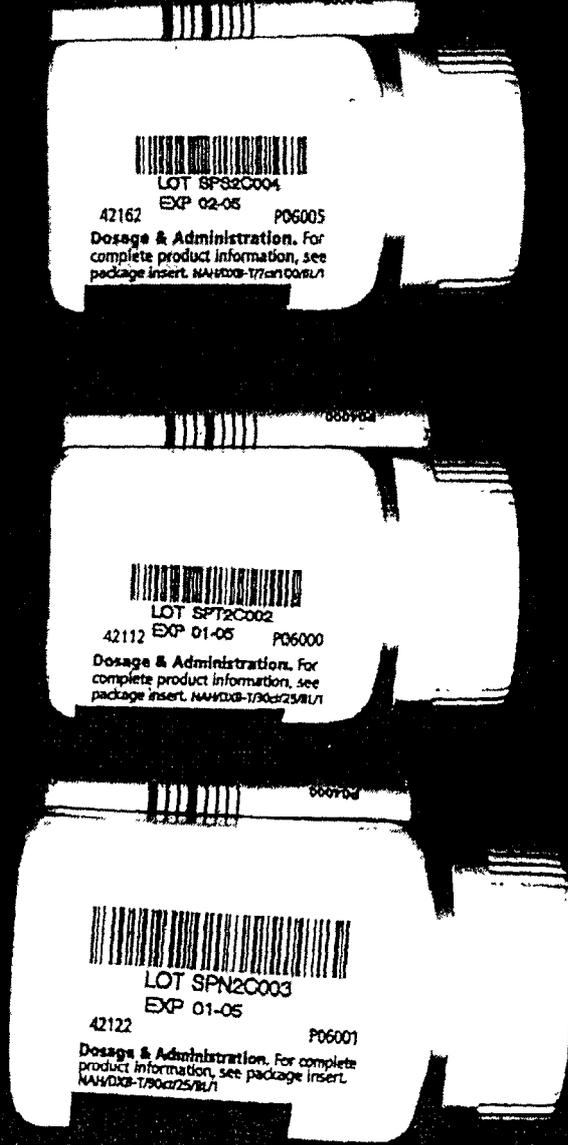
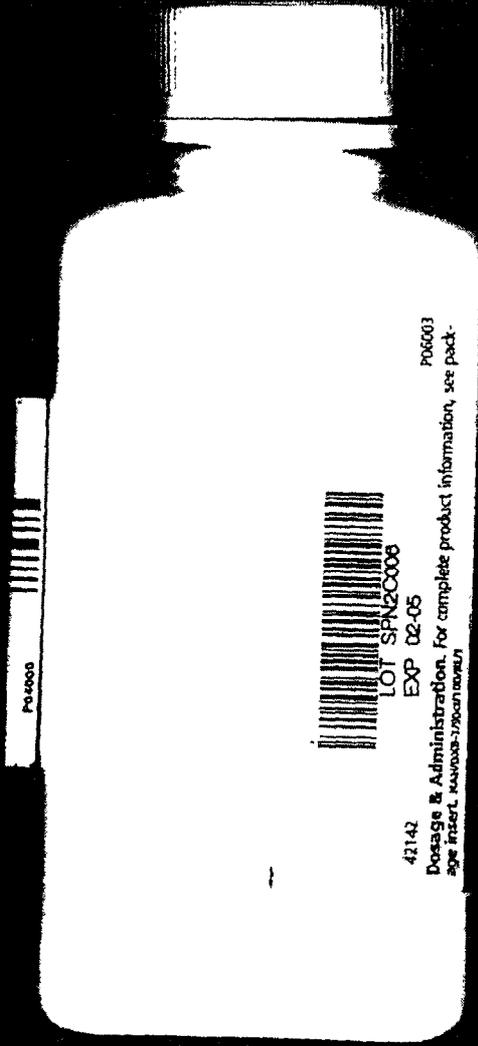


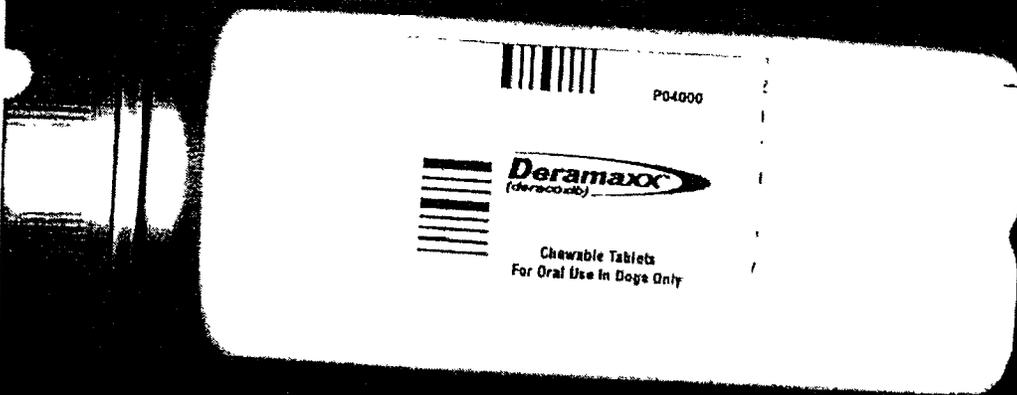
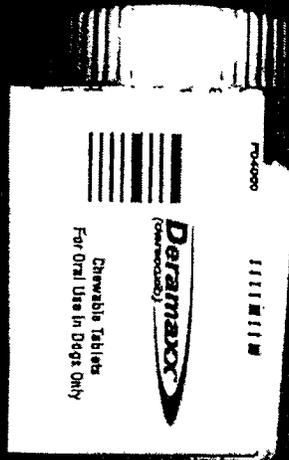
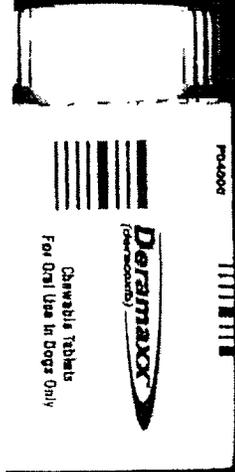
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P06005
42162
Dosage & Administration. For complete product information, see package insert. NADA#141-203/100BU1

Deramaxx™
(deracoxib)

7 chewable tablets

A coxib-class NSAID
For Use in Dogs Only

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

NADA#141-203, Approved by FDA.
Manufactured for Novartis Animal Health US, Inc. Greensboro, NC 27408

NOVARTIS **100 mg**

Storage Conditions: Store at room temperature between 59° and 86°F (15-30°C). **WARNINGS:** Keep this and all medications out of the reach of children.



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P06002
42132
Dosage & Administration. For complete product information, see package insert. NADA#141-203/100BU1

Deramaxx™
(deracoxib)

30 chewable tablets

A coxib-class NSAID
For Use in Dogs Only

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

NADA#141-203, Approved by FDA.
Manufactured for Novartis Animal Health US, Inc. Greensboro, NC 27408

NOVARTIS **100 mg**

Storage Conditions: Store at room temperature between 59° and 86°F (15-30°C). **WARNINGS:** Keep this and all medications out of the reach of children.



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P06003
42142
Dosage & Administration. For complete product information, see package insert. NADA#141-203/100BU1

Deramaxx™
(deracoxib)

90 chewable tablets

A coxib-class NSAID
For Use in Dogs Only

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

NADA#141-203, Approved by FDA.
Manufactured for Novartis Animal Health US, Inc. Greensboro, NC 27408

NOVARTIS **100 mg**

Storage Conditions: Store at room temperature between 59° and 86°F (15-30°C). **WARNINGS:** Keep this and all medications out of the reach of children.



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42122

P06001

Dosage & Administration. For complete product information, see package insert. NAH/DXB-1790ct/25/BU1

90 chewable tablets
A coxib-class NSAID
For Use in Dogs Only
Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.
NADA#141-203. Approved by FDA.
Manufactured for Novartis Animal Health US, Inc. Greensboro, NC 27408
NOVARTIS
25 mg

Deramaxx
(deracoxib)

Storage Conditions: Store at room temperature between 59° and 86°F (15-30°C).

WARNINGS: Keep this and all medications out of the reach of children.



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42112

P06000

Dosage & Administration. For complete product information, see package insert. NAH/DXB-1730ct/25/BU1

30 chewable tablets
A coxib-class NSAID
For Use in Dogs Only
Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.
NADA#141-203. Approved by FDA.
Manufactured for Novartis Animal Health US, Inc. Greensboro, NC 27408
NOVARTIS
25 mg

Deramaxx
(deracoxib)

Storage Conditions: Store at room temperature between 59° and 86°F (15-30°C). **WARNINGS:** Keep this and all medications out of the reach of children.



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42152

P06004

Dosage & Administration. For complete product information, see package insert. NAH/DXB-177ct/25/BU1

7 chewable tablets
A coxib-class NSAID
For Use in Dogs Only
Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.
NADA#141-203. Approved by FDA.
Manufactured for Novartis Animal Health US, Inc. Greensboro, NC 27408
NOVARTIS
25 mg

Deramaxx
(deracoxib)

Storage Conditions: Store at room temperature between 59° and 86°F (15-30°C). **WARNINGS:** Keep this and all medications out of the reach of children.



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