





DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAY 13 2004

NADA 141-186 E-0013

IDEXX Pharmaceuticals, Inc.
Attention: Randy C. Lynn, DVM, MS, DACVCP
Director of Regulatory Affairs
4249 Piedmont Parkway, Suite 105
Greensboro, North Carolina 27410

received
5-21-04

Dear Dr. Lynn:

In an original new animal drug application (NADA) dated August 26, 2003 (E0013), and amended December 2, 2003 (T0014), February 23, 2004 (T0015), February 24, 2004 (T0016), March 3, 2004 (T0017), and March 19, 2004 (T0018), you requested approval of SURPASS (1% diclofenac sodium) topical antiinflammatory cream, indicated for the control of pain and inflammation associated with osteoarthritis (OA) in tarsal, carpal, metacarpophalangeal, metatarsophalangeal, and proximal interphalangeal (hock, knee, fetlock, and pastern) joints in horses.

Your application is approved. A notice of this approval is being forwarded for publication in the FEDERAL REGISTER. Prior to distribution and marketing, three copies of each component of the final printed labeling must be submitted to CVM. This labeling should be identical to the facsimile labeling submitted on March 19, 2004 (T0018).

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.

Manufacturing process validation is required under GMPs (21 CFR Parts 211 and 226). A product that does not conform to GMPs is adulterated (21 USC 351(a)(1)(B)). If manufacturing process validation information was not available or was found deficient at the time of the pre-approval inspection, the appropriate FDA District Office should be contacted after such validation has been completed on production lots and prior to shipment of the drug product. FDA may take regulatory action if drug products are shipped prior to completion of the validation process.

An expiration dating of 24 months is acceptable for this product.

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If you submit any correspondence in the future relating to this approval, you should include a citation to this letter by date and NADA number. Any request to change the conditions of approval may require the submission of a supplemental application. If you have any questions, please contact Dr. Melanie R. Berson, Director, Division of Therapeutic Drugs for Non-Food Animals, at 301-827-7540.

Sincerely yours,



Stephen F. Sundlof, D.V.M., Ph.D.
Director, Center for Veterinary Medicine

Enclosure: Freedom of Information Summary

Date of Approval: **MAY 13 2004**

FREEDOM OF INFORMATION SUMMARY

NADA 141-186

SURPASS
(1% diclofenac sodium)

SURPASS is indicated for the control of pain and inflammation associated with osteoarthritis (OA) in tarsal, carpal, metacarpophalangeal, metatarsophalangeal, and proximal interphalangeal (hock, knee, fetlock, and pastern) joints in horses.

Sponsored by:
IDEXX Pharmaceuticals, Inc.

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1. GENERAL INFORMATION:

- a. File Number: NADA 141-186
- b. Sponsor: IDEXX Pharmaceuticals, Inc.
4249-105 Piedmont Pkwy.
Greensboro, NC 27410
- Drug Labeler Code: 065274
- c. Established Name: 1% diclofenac sodium
- d. Proprietary Name: SURPASS
- e. Dosage Form: topical cream
- f. How Supplied: 124 gram trilaminate tubes
- g. How Dispensed: Rx
- h. Amount of Active Ingredients: 1% diclofenac sodium
- i. Route of Administration: topical
- j. Species/Class: horse
- k. Recommended Dosage: Wear rubber gloves to prevent absorption into the hands. Apply a five-inch (5") ribbon of cream twice daily over the affected joint for up to five days. Rub the cream thoroughly into the hair covering the joint until it disappears.
- l. Pharmacological Category: nonsteroidal anti-inflammatory drug (NSAID)
- m. Indications: SURPASS is indicated for the control of pain and inflammation associated with osteoarthritis (OA) in tarsal, carpal, metacarpophalangeal, metatarsophalangeal, and proximal interphalangeal (hock, knee, fetlock, and pastern) joints in horses.

2. EFFECTIVENESS:

a. Dosage Characterization:

Seventeen horses received topical diclofenac once daily for five days (18 horses received placebo). The applied dose was estimated as a three-inch ribbon of test article cream (as measured against a three inch piece of paper), and administered topically once a day to the 35 horses. Following the study, tube weights were used to determine the actual dose that each horse received. Horses received an average dose of 100 mg diclofenac once daily (doses ranged from 38 to 136 mg per day).

variable	placebo	diclofenac
lameness improved	10/18 (55%)	8/17 (47%)

The primary variable for the demonstration of effectiveness was the subjective evaluation of lameness by study investigators. After five days of treatment, lameness examinations did not show effectiveness for diclofenac; therefore, the study protocol was amended to provide twice daily administration (the dose was doubled).

The twice daily treatment portion of the study comprised the field study (see SUBSTANTIAL EVIDENCE section below), and confirmed the effectiveness of the twice daily dosage. In the field study, horses received a mean dose of 73 mg per application (the amount of diclofenac in mg that is contained in 5 inches of cream).

The twenty-eight day Target Animal Safety study evaluated SURPASS for approximately three times the labeled duration of administration (see TARGET ANIMAL SAFETY section below).

Therefore, the effective dose is 5 inches (73 mg) of 1% diclofenac topical anti-inflammatory cream, administered twice daily for up to ten days.

b. Substantial Evidence:

Title: Placebo-controlled FIELD STUDY to evaluate the safety and effectiveness of topically applied 1% diclofenac anti-inflammatory cream for the control of pain and inflammation associated with osteoarthritis (OA) in horses (BRP-DEQ-02/twice daily results).

Investigators/Study Locations:

William P. Diehl, DVM Mayo and Rofe Equine Clinic Middleburg, VA	Mike Parker, DVM Walnut Creek, CA
John M. Donecker, VMD, MS, DABVP Reidsville, NC	Bradley S. Root, DVM Albuquerque Equine Center Albuquerque, NM
Dan Flynn, VMD Georgetown Equine Hospital Charlottesville, VA	Roger Sifferman, DVM Bradford Park Veterinary Hospital Springfield, MO
Richard Henninger, DVM, MS, DACVS, DABVP University Equine Veterinary Services Findlay, OH	Barbara Lynn Smith, DVM, MS, PhD, DACVS Corvallis, OR
Jim Mitchell, DVM Cream Ridge, NJ	Nick Vatisstas, BVSc, PhD, DACVS, MRCVS Vacaville, CA
Scott A. Nebergall, DVM Arthur, IL	

Animals: A total of 82 client-owned horses diagnosed with osteoarthritis (by lameness examination and radiography) were included in the final analysis of the field study. Horses (51 geldings, 28 mares and 3 stallions), ranging in age from 2 to 30 years, were treated with test cream. Forty-two horses were treated twice daily with 1% diclofenac topical anti-inflammatory cream; forty horses received placebo cream.

Descriptions of osteoarthritic conditions in the 82 horses are listed in the following table:

		Placebo (n=40)	Diclofenac (n=42)
Study Joint	Carpus (knee)	5	8
	Tarsus (hock)	16	18
	Stifle	0	1
	Pastern	5	8
	Fetlock	14	7
Study Leg	Left Side	26	19
	Right Side	14	23
	Forelimb	22	22
	Hindlimb	18	20
Disease Duration	Chronic (>1 month)	37	37
	Acute (<1 month)	3	4
	Unknown	0	1
Mean Duration	Months (min-max)	25.0 (0.5-120)	21.1 (0.13-120)
Disease Severity	Mild	16	20
	Moderate	14	12
	Severe	10	10

Treatment Groups: Horses received either diclofenac 1% cream or placebo cream, rubbed into the hair on the affected joints until the cream disappeared.

Dosage: Horses received a mean dose of 73 mg of diclofenac (ranging from 27 to 111 mg per application), twice daily. Actual dose received was determined by tube weight measurements for each horse, and is equivalent to the application of a five-inch ribbon of cream.

Route of Administration: topical

Frequency and Duration of Treatment: twice daily for five days

Variables Measured:

Investigators examined the horses on days 1 (baseline), 2, 3, 4 and 5 and recorded lameness, pain and mobility scores. The scores were evaluated statistically. The horse owner also evaluated the horse daily for lameness each day. The investigator applied at least one of the two daily treatments. Blood samples were collected for hematology and serum chemistry on days 0 and 5.

The primary variable for success was lameness examination by the veterinarian. Criteria for success for each variable was met when improvement by at least one score point was noted. Scores for each variable were assigned as follows:

Lameness (primary variable):

- 0 = lameness not perceptible under any circumstances
- 1 = lameness is difficult to observe and not consistently apparent, regardless of circumstances (for example, weight carrying, circling, inclines, hard surfaces, etc.)
- 2 = lameness is difficult to observe at a walk or when trotting in a straight line, but is consistently apparent under certain circumstances (for example, weight carrying, circling, jogging on inclined or hard surfaces)
- 3 = lameness is consistently observable at a trot under all circumstances
- 4 = lameness is obvious at a walk
- 5 = lameness produces minimal weight bearing in motion and/or at rest or a complete inability to move

Joint pain:

The joint was manipulated through a normal range of motion and subjectively scored:

- 0 = no pain
- 1 = mild pain (horse calmly withdraws limb)
- 2 = moderate pain (horse withdraws limb and exhibits some signs of distress)
- 3 = severe pain (horse withdraws limb and exhibits severe distress)

Joint mobility:

The joint was manipulated through a normal range of motion and subjectively scored in comparison to Day 0:

0 = no change from Day 0
 1 = 5-10% improvement from Day 0
 2 = 11-20% improvement from Day 0
 3 = >20% improvement from Day 0

Evaluation by horse owner in comparison to Day 0:

0 = worse
 1 = no change from Day 0
 2 = slight improvement from Day 0
 3 = much improvement from Day 0
 4 = normal (no signs of pain, stiffness or lameness)

Statistical Methods: The percentage of horses that improved in each group was evaluated with an exact test of the common odds ratio, stratified by investigator, with a two-tailed α of 0.05.

Results: The percentage of horses treated with twice daily diclofenac that showed improvement in lameness score was significantly greater than the percentage of horses in the placebo group ($p=0.0059$). Seventy-four percent of horses treated with twice daily diclofenac showed improvement in lameness, while 40% of horses treated with placebo showed improvement.

Variable	Placebo	Diclofenac	p-value
	Number of horses showing improvement by at least one grade / Total number of evaluable horses		
Lameness Improved	16/40 (40%)	31/42 (74%)	$p = 0.0059$
Pain Improved	15/40 (38%)	20/42 (48%)	$p = 0.4507$
Mobility Improved	9/40 (23%)	12/42 (29%)	$p = 0.3887$
Improvement Noted by Owner	20/40 (50%)	30/41 (73%)	$p = 0.0950$

Bloodwork: Day 5 blood samples for one investigator (19 horses) were not immediately analyzed, resulting in artifacts in the results for glucose, phosphorus, potassium, hemoglobin, hematocrit, and red blood cell levels. Therefore, post-treatment results were not available for 19 horses for these bloodwork parameters.

During the study, no clinically relevant abnormalities were identified from hematology or serum chemistry samples (comparing baseline to day 5), except for one horse that colicked (see adverse reactions). Day 5 bloodwork for this horse showed decreases in RBC, Hb, and HCT, with an increase in PMNs (compared to pretreatment values):

blood parameter	pretreatment (day 1)	day 5	laboratory reference values
HCT (%)	45.9	27.1	37-55
RBC ($\times 10^6/\mu\text{l}$)	8.35	5.13	4.5-7.5
Hb (g/dl)	16.1	9.6	12-18
PMNs ($\times 10^3/\mu\text{l}$)	50	78	50-77

Adverse Reactions: One diclofenac-treated horse developed colic and responded to symptomatic treatment on day four of the study. One horse treated with placebo exhibited mildly jaundiced mucous membranes on day five; bloodwork for this horse was unremarkable. No other adverse reactions were noted during the study.

Conclusions: The study demonstrated an improvement in clinical lameness associated with OA in horses when diclofenac was administered twice a day. Adverse reactions were not definitively attributed to the use of diclofenac 1% cream.

3. **TARGET ANIMAL SAFETY:**

Title: Target Animal Safety Study of 1% diclofenac sodium topical anti-inflammatory cream applied topically to horses (study # 98308h, BRP-DEQ-06)

Purpose: To evaluate the safety in horses of three dosage levels (0.6X, 1.7X, and 2.8X) of 1% diclofenac sodium topical anti-inflammatory cream in a 28 day study. An additional group received 5.6X the recommended dose, given on a single day, and followed by a 14 day observation period.

Investigator: John W. Campbell, Ph.D.

Study Location: Southwest Bio-Labs, Inc.
Las Cruces, NM

Animals: Thirty horses (15 geldings and 15 mares), approximately 3 to 18 years old, six horses per group (3 geldings and 3 mares).

Dosage Groups:

treatment group	no. of horses	diclofenac daily dose (mg*)	no. of diclofenac-treated joints/day
1	6	0 (0X)	0 (sham-dosed)
2	6	82 (0.6X)	1
3	6	246 (1.7X)	3
4	6	410 (2.8X)	5
5	6	820 (5.6X)	10 (5 joints treated twice on a single day)

*Based on tube weight measurements per group, the average dose per application contained 41 mg diclofenac.

Route of Administration: Topical

Frequency of Treatment:

Groups 1-4: Treated every day for 28 consecutive days

Group 5: Treated for a single day, followed by a 14 day untreated observation period.

Duration of Study: 28 days for groups 1-4; 14 days for group 5.

Variables measured:

Groups 1 through 4:

-Clinical examinations were conducted on days 5, 12 and 19, and a complete physical examination was conducted prior to treatment and at termination.

-Horses were observed once daily for clinical abnormalities.

-Body weights were recorded on days -8, -1, 5, 12, 19 and prior to termination.

-Hematology and serum chemistry samples were drawn on days -3, 6, 13, 20 and 27 or 28 (Note: GGT, fibrinogen, and bleeding times were not evaluated during the study).

-Urinalyses (midstream) were performed on days -2 or -1 and 27 or 28.

-Feces were evaluated (blood, color, consistency, parasites, other abnormalities) on days -2 or -1 and 28.

-Synovial fluid was withdrawn from one joint prior to treatment. During necropsy, each horse had one treated and one contralateral untreated joint sampled.

-Necropsy: Gross pathology and histopathology were evaluated in all horses.

Limited histopathology results were obtained from horses in groups 2 and 3 (dermal tissue, liver, stomach, all sections of the intestinal tract, treated and untreated joints, and uterus).

Group 5:

Variables for the 5.6X group were the same. Results for this group were compared to placebo results.

- Clinical examinations were conducted on day 4, and a complete physical examination was conducted prior to treatment and at termination.
- Horses were observed once daily for clinical abnormalities.
- Body weights were recorded prior to the study, days 4 and 13.
- Hematology and serum chemistry samples were drawn prior to study, day 5 and 12 (Note: GGT, fibrinogen, and bleeding times were not evaluated during the study).
- Urinalyses (midstream) were performed prior to study and day 12 or 13.
- Feces were evaluated (blood, color, consistency, parasites, other abnormalities) prior to study and day 13.
- Synovial fluid was withdrawn from one joint prior to treatment. During necropsy, each horse had one treated and one untreated joint sampled.
- Necropsy: Gross pathology and histopathology were evaluated in all horses.

Results:

Weight loss: One horse in the 2.8X treatment group had increased GI sounds prior to treatment and broke with diarrhea during the study, losing a total of 20 kg (the most weight lost by any horse in groups 1 through 4). Necropsy of the GI tract of this horse was normal; no signs of GI parasitism were noted.

Horses in the 5.6X treatment group (single administration) lost more weight per horse over 14 days compared to the other 4 treatment groups. Four of six horses in the 5.6X group lost weight during the 14 day study (between 13 and 29 kg). One of these horses exhibited signs of upper respiratory illness prior to treatment (cough, nasal discharge, elevated WBC count), and showed clinical improvement during the study. Evidence of strongyle parasitism was also noted at termination in this horse. The other three horses in this group that lost weight did not show other clinical signs or evidence of inappetence.

Gastric ulcer: Gross necropsy of one horse in the 5.6X group showed a thickened stomach wall and an ulcer (1x3 cm) in the glandular portion of the stomach. Histologically, the ulcerated area showed chronic mild inflammation, mild fibrosis and fibroplasia. Other clinical signs associated with NSAID toxicity (colonic ulceration, hypoproteinemia, hypoalbuminemia) were not noted in this horse.

Joint fluid: The synovial fluid of one horse in the 2.8X dosage group contained elevated WBCs at termination, possibly the result of pretreatment removal of joint fluid. This horse did not show other abnormal clinical signs.

Plasma concentrations of diclofenac following topical administration: Dose dependent increases in blood levels of diclofenac were detected in horses at 1.7X (three of six horses) and 2.8X (six of six horses) the recommended dose.

Conclusions:

The correlation of clinical pathology results with clinical observations and necropsy results did not reveal any individual horses showing definitive signs of NSAID toxicity. It should be noted that clinical pathology results did not include an evaluation of GGT, fibrinogen, or bleeding times.

Clinical signs of illness during the study that may have been related to the administration of diclofenac were weight loss in 4 (of 6) horses in the 5.6X group, and possible exacerbation of existing gastrointestinal (GI) disturbances in one horse in the 2.8X group. The etiology of the glandular gastric ulcer in the 5.6X group remains unknown.

4. HUMAN SAFETY:

This drug is intended for use in horses, 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 horses intended for human consumption.

User Safety: Keep out of reach of children. Not for human use. Consult a physician in case of accidental ingestion by humans. Wear gloves to prevent absorption into the hands. Direct contact with the skin should be avoided. If contact occurs, the skin should be washed immediately with soap and water.

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 SURPASS when used under the labeled conditions of use is safe and effective for the control of pain and inflammation associated with osteoarthritis (OA) in tarsal, carpal, metacarpophalangeal, metatarsophalangeal and proximal interphalangeal (hock, knee, fetlock and pastern) joints in horses.

The drug is restricted to use by or on the order of a licensed veterinarian because professional veterinary expertise is required to diagnose equine osteoarthritis and to monitor response to treatment.

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.

SURPASS (1% diclofenac sodium) Topical Anti-Inflammatory Cream is under the following U.S. patent numbers:

US 4,761,288 expires August, 2, 2005

US 4,897,269 expires January, 30, 2007

US 4,937,078 expires June, 26, 2007

6. ATTACHMENTS:

Facsimile labeling is attached as indicated below:

- a. Package Insert
- b. Client Information Sheet
- c. Tube Label
- d. Box Label
- e. Display Box Label