

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<br>(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<br>Mayo and Rofe Equine Clinic<br>Middleburg, VA                              | Mike Parker, DVM<br>Walnut Creek, CA   |
| John M. Donecker, VMD, MS, DABVP<br>Reidsville, NC  | Bradley S. Root, DVM<br>Albuquerque Equine Center<br>Albuquerque, NM         |
| Dan Flynn, VMD<br>Georgetown Equine Hospital<br>Charlottesville, VA                                 | Roger Sifferman, DVM<br>Bradford Park Veterinary Hospital<br>Springfield, MO |
| Richard Henninger, DVM, MS,<br>DACVS, DABVP<br>University Equine Veterinary Services<br>Findlay, OH | Barbara Lynn Smith, DVM, MS, PhD,<br>DACVS<br>Corvallis, OR                  |
| Jim Mitchell, DVM<br>Cream Ridge, NJ  | Nick Vatistas, BVSc, PhD, DACVS, MRCVS<br>Vacaville, CA                      |
| Scott A. Nebergall, DVM<br>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  $\alpha$  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):

| <b>blood parameter</b>       | <b>pretreatment (day 1)</b> | <b>day 5</b> | <b>laboratory reference values</b> |
|------------------------------|-----------------------------|--------------|------------------------------------|
| HCT (%)                      | 45.9                        | 27.1         | 37-55                              |
| RBC (x 10 <sup>6</sup> /μl)  | 8.35                        | 5.13         | 4.5-7.5                            |
| Hb (g/dl)                    | 16.1                        | 9.6          | 12-18                              |
| PMNs (x 10 <sup>3</sup> /μl) | 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

# VET INSERT/CLIENT INFORMATION SHEET



## Veterinary Package Insert

**SURPASS™**

(1% diclofenac sodium)

Topical Anti-Inflammatory Cream for Use in Horses

### CAUTION

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

### DESCRIPTION

SURPASS™ topical cream contains 1% diclofenac sodium. Diclofenac is a nonsteroidal anti-inflammatory drug of the phenylacetic acid class. The chemical name for diclofenac is sodium [o-(2,6-dichloroanilino)phenyl]acetate. The empirical formula is  $C_{14}H_{10}Cl_2NNaO_2$  and the molecular weight is 318.13. SURPASS topical cream contains 1% diclofenac sodium in a base composed of Phospholipon 90H, propylene glycol, alcohol (5.94%), vitamin E acetate, benzethonium chloride and purified water in a liposomal formulation.

### INDICATIONS

SURPASS topical cream 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.

### DOSAGE AND ADMINISTRATION

Always provide the Client Information Sheet with the prescription.

*Dosage:* Apply a five-inch (5") ribbon of SURPASS topical cream twice daily over the affected joint for up to ten days.

*Administration:* Wear rubber gloves to prevent absorption into the hands. Rub the cream thoroughly into the hair covering the joint until it disappears.

### CONTRAINDICATIONS

SURPASS topical cream is contraindicated in animals with known hypersensitivity to diclofenac.

### WARNINGS

**Not for 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.

*Animal Safety:* For topical use in horses only. Owners should be advised to observe for signs of potential drug toxicity (see INFORMATION FOR OWNER OR PERSON TREATING ANIMAL and ADVERSE REACTIONS).

### PRECAUTIONS

Exceeding the recommended dosage or treating multiple joints may increase plasma concentrations of diclofenac (see ANIMAL SAFETY). The systemic effects of excess diclofenac doses that exceed the recommended label amount and duration have not been evaluated.

Horses should undergo a thorough history and physical examination before initiation of NSAID therapy. Appropriate laboratory tests should be conducted to establish hematological and serum biochemical baseline data before and periodically during administration of any NSAID. Owners should be advised to observe for signs of potential drug toxicity (see INFORMATION FOR OWNER OR PERSON TREATING ANIMAL).

Treatment with SURPASS should be terminated if signs such as inappetence, colic, fecal abnormalities, anemia or depression are observed.

As a class, NSAIDs may be associated with gastrointestinal and renal toxicity. When NSAIDs inhibit prostaglandins that cause inflammation, they may also inhibit prostaglandins that maintain normal homeostatic function. These anti-prostaglandin effects may result in clinically significant disease in patients with underlying or preexisting disease more often than in healthy patients. Patients at greatest risk for renal toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with renal, cardiovascular and/or hepatic dysfunction.

Studies to determine the effect of SURPASS when administered concomitantly with other drugs have not been conducted. Since many NSAIDs possess the potential to induce gastric ulceration, concomitant use of SURPASS with any other anti-inflammatory drugs, such as other NSAIDs and corticosteroids, should be avoided. Drug compatibility should be monitored closely in patients receiving adjunctive therapy.

The safety of SURPASS has not been investigated in breeding, pregnant or lactating horses, or in horses under one year of age.

### ADVERSE REACTIONS

During the field study, one diclofenac-treated horse developed colic on day four of the study and responded to symptomatic treatment. One placebo-treated horse exhibited mildly jaundiced mucous membranes on day five. Adverse reactions during the



## Client Information Sheet

**SURPASS™**

(1% diclofenac sodium)

Topical Anti-Inflammatory Cream for Use in Horses

This summary contains important information about SURPASS™ topical cream. You should read this information before treating your horse with SURPASS. This sheet of information is provided only as a summary and does not take the place of instructions from your veterinarian. Talk to your veterinarian if you have any questions about this information or to learn more about SURPASS.

### 1. What is SURPASS topical cream?

SURPASS topical cream contains 1% diclofenac sodium. Diclofenac is a prescription non-narcotic, nonsteroidal anti-inflammatory drug (NSAID) that controls pain. Diclofenac is used for the control of pain and inflammation associated with osteoarthritis (OA) in hock, knee, fetlock or pastern joints in horses.

### 3. Which horses should not receive treatment with SURPASS?

SURPASS is for topical use in horses only. SURPASS should not be used in horses exhibiting allergic reactions to diclofenac. SURPASS is not for use in horses intended for food. The safety of SURPASS has not been determined in horses less than one year of age, in horses used for breeding, pregnant mares, or mares nursing foals.

### 4. How do I apply SURPASS to my horse?

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. Apply a five-inch (5") ribbon of SURPASS twice daily over the affected



# VET INSERT/CLIENT INFORMATION SHEET



## Veterinary Package Insert

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### WARNINGS

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Studies to determine the effect of SURPASS when administered concomitantly with other drugs have not been conducted. Since many NSAIDs possess the potential to induce gastric ulceration, concomitant use of SURPASS with any other anti-inflammatory drugs, such as other NSAIDs and corticosteroids, should be avoided. Drug compatibility should be monitored closely in patients receiving adjunctive therapy.

The safety of SURPASS has not been investigated in breeding, pregnant or lactating horses, or in horses under one year of age.

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### 2. What kind of results can I expect when my horse is being treated with SURPASS?

Osteoarthritis is a painful condition caused by the progressive deterioration of the cartilage, accompanied by changes in the bone and soft tissues of the joint. This disease is characterized by pain and loss of function of the affected joint.

While SURPASS is not a cure for osteoarthritis, it does control the pain and inflammation associated with OA and increases the horse's mobility. The response to SURPASS will vary from horse to horse. In most horses, maximum improvement is seen in less than one week.

### 3. Which horses should not receive treatment with SURPASS?

SURPASS is for topical use in horses only. SURPASS should not be used in horses exhibiting allergic reactions to diclofenac. SURPASS is not for use in horses intended for food. The safety of SURPASS has not been determined in horses less than one year of age, in horses used for breeding, pregnant mares, or mares nursing foals.

### 4. How do I apply SURPASS to my horse?

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. Apply a five-inch (5") ribbon of SURPASS twice daily over the affected joint for up to ten days. Rub it thoroughly into the hair covering the joint until it disappears.

### 5. What should I tell my veterinarian?

Tell your veterinarian if your horse has experienced allergic reactions to diclofenac or other medications. Tell your veterinarian if your horse is pregnant or nursing a foal, or if you intend to breed the horse. Tell your veterinarian if your horse has ever been diagnosed with an ulcer.

### 6. What possible side effects may occur in my horse's therapy?

Horses should undergo a thorough history and physical examination by a veterinarian before the initiation of any SURPASS therapy.

safety study included a gastric ulcer in one horse that received 5.6X the recommended dosage, diarrhea and uterine discharge in one horse that received 2.8X the recommended dosage, and weight loss in four of the six horses in the 5.6X dosage group.

To report suspected adverse reactions, to obtain a Material Safety Data Sheet or for technical assistance, call 1-800-374-8006.

#### INFORMATION FOR OWNER OR PERSON TREATING ANIMAL

Owners should be advised of the potential for adverse reactions and be informed of the clinical signs associated with NSAID intolerance. Adverse reactions may include weight loss, colic, diarrhea, or icterus. Serious adverse reactions associated with this drug class can occur without warning and, in rare situations, result in death. Owners should be advised to discontinue NSAID therapy and contact their veterinarian immediately if signs of intolerance are observed. The majority of patients with drug-related adverse reactions recover when the signs are recognized, drug administration is stopped, and veterinary care is initiated.

#### CLINICAL PHARMACOLOGY

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic properties. The mechanism of action of diclofenac, like other NSAIDs, is believed to be associated with the inhibition of cyclooxygenase activity.

#### EFFECTIVENESS

In a controlled field study, 82 horses with osteoarthritis were treated with SURPASS (42 horses) or placebo (40 horses). Lameness examinations were performed in horses with osteoarthritis associated with the tarsal, carpal, metacarpophalangeal, metatarsophalangeal and proximal interphalangeal joints. Investigators were masked to treatment. Investigators and owners were instructed to apply the test article over the affected joint twice daily (BID) for five days. Actual doses received by individual horses were calculated using tube weight measurements. The mean dose applied during the study was 73 mg per application. Average lameness scores showed statistically significant improvement following treatment with SURPASS topical cream.

One diclofenac-treated horse developed colic and responded to symptomatic treatment on day four of the study. Day five bloodwork for the horse that colicked showed decreases in RBC, Hb and HCT, with an increase in PMNs, compared to pretreatment values. One placebo-treated horse exhibited mildly jaundiced mucous membranes on day five. No other adverse reactions were noted during the study.

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Using more than the recommended amount of SURPASS (for example, by treating multiple joints) has not been tested and is not recommended. Excessive doses to the skin have been shown to enter the bloodstream and this may increase the risk of side effects. Adverse reactions associated with NSAIDs may include weight loss, colic, diarrhea, or yellowing of the gums, skin, or whites of the eyes (jaundice). Serious adverse reactions associated with this drug class can occur without warning and, in rare situations, result in death. Discontinue the use of SURPASS and contact your veterinarian immediately if these signs are observed. The majority of patients with drug-related adverse reactions recover when the signs are recognized, drug administration is stopped, and veterinary care, if appropriate, is initiated.

#### 7. What precautions should I take before administering SURPASS topical cream?

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.

**SURPASS topical cream should only be applied to horses.** Keep SURPASS and all medications out of the reach of children. SURPASS is not for human use. Contact a physician in case of accidental ingestion by people.

#### 8. Can SURPASS be given with other medications?

SURPASS should not be given with any other anti-inflammatory drugs, such as other NSAIDs (for example, aspirin, phenylbutazone, flunixin) and corticosteroids (for example, cortisone, prednisone, dexamethasone, triamcinolone). Tell your veterinarian about all medicines that you are planning to administer in addition to SURPASS. These should include other medications that you can obtain without a prescription.

#### ANIMAL SAFETY

A controlled safety study was conducted with SURPASS topical cream. Four groups of six healthy adult horses received 0, 0.6, 1.7 or 2.8X the recommended daily dose for twenty-eight days. The daily dose was divided into two applications on day one of the study. For the remainder of the study, the entire daily dose was given at one time on 0, 1, 3 or 5 joints (tarsal, carpal, metacarpophalangeal, metatarsophalangeal, and proximal interphalangeal joints), depending on the dosage group. The control group of six horses was sham-dosed by rubbing the joints daily for twenty-eight days. An additional study group evaluated six horses that received 5.6X the recommended daily dose of SURPASS topical cream distributed over five joints on a single day. This dose group was observed for fourteen days without additional treatment.

Clinical examinations, hematology, serum chemistry, synovial fluid analyses, gross necropsy and histopathology were performed. At necropsy, one horse in the 5.6X group had a glandular gastric ulcer. A horse in the 2.8X group had diarrhea and uterine discharge throughout the study. Four of the six horses in the 5.6X group lost weight during the study.

Dose-dependent increases in diclofenac plasma concentrations were detected in horses in the 1.7X and 2.8X treatment groups.

#### STORAGE INFORMATION

Store at up to 25°C (77°F). Protect from freezing.

#### HOW SUPPLIED

SURPASS topical cream is white to pinkish-white and is packaged in 124-gram trilaminate tubes.

NADA #141-186. Approved by FDA.

SURPASS is a trademark of IDEXX Pharmaceuticals, Inc.

Manufactured for: IDEXX Pharmaceuticals, Inc.  
Greensboro, North Carolina 27410 USA

Manufactured under U.S. Patent No. 4,937,078.

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IPI/DIC/PI/19 3/04 000100

**IDEXX**  
LABORATORIES

Greensboro, NC 27410 USA

#### 9. How should I store SURPASS?

Store at up to 25°C (77°F). Protect from freezing. Keep SURPASS and all medications out of reach of children.

#### 10. What else should I know about SURPASS?

This document provides a summary of information about SURPASS. If you have questions or concerns about SURPASS or osteoarthritis pain, talk to your veterinarian.

As with all prescription medications, SURPASS should only be administered to the patient for whom it was prescribed, and should only be used as prescribed.

To report a suspected adverse reaction, call 1-800-374-8006.

SURPASS is a trademark of IDEXX Pharmaceuticals, Inc.

SURPASS is manufactured for:  
IDEXX Pharmaceuticals, Inc.  
Greensboro, North Carolina 27410 USA

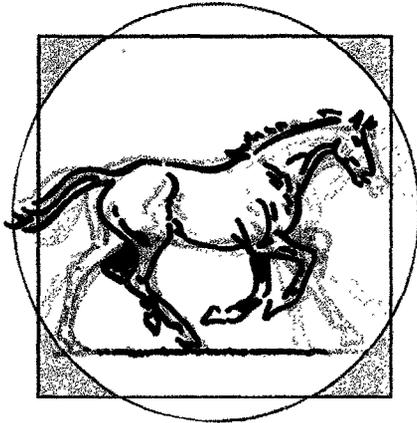
Manufactured under U.S. Patent No. 4,937,078.

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**IDEXX**  
LABORATORIES

Greensboro, NC 27410 USA



# SURPASS™

(1% diclofenac sodium)

Topical Anti-Inflammatory Cream for Use in Horses

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

Net wt. 124 grams

**WARNING:** Not for horses intended for human consumption. Keep out of reach of children. Not for use in humans.

**INDICATIONS:** SURPASS topical cream 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.

**DOSAGE AND ADMINISTRATION:** Wear rubber gloves to prevent absorption into the hands. Apply a five-inch ribbon of cream twice daily over the affected joint for up to ten days. Rub it thoroughly into the hair covering the joint until it disappears.

Read accompanying package insert before use.

**STORAGE INFORMATION:** Store at up to 25°C (77°F). Protect from freezing.

SURPASS topical cream contains 1% diclofenac sodium in a base composed of Phospholipon 90H, propylene glycol, alcohol (5.94%), vitamin E acetate, benzethonium chloride and purified water in a liposomal formulation.

SURPASS is manufactured for IDEXX Pharmaceuticals, Inc., Greensboro, NC 27410 USA.

SURPASS is a trademark of IDEXX Pharmaceuticals, Inc.

Manufactured under U.S. Patent No. 4,937,078.

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NADA 141-186, Approved by FDA

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**IDEXX**  
LABORATORIES



NOTE: The lot number and expiration date will be embossed into the crimp at the end of the tube.

TUBE

Binary Code #111

**WARNING: Not for horses intended for human consumption. Keep out of the reach of children. Not for use in humans.**

**INDICATIONS:** SURPASS topical cream 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.

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Manufactured under U.S. Patent No. 4,937,078.

SURPASS is manufactured for IDEXX Pharmaceuticals, Inc., Greensboro, NC 27410 USA.

SURPASS is a trademark of IDEXX Pharmaceuticals, Inc.

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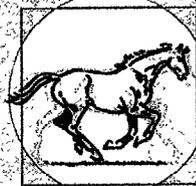
NADA 141-186. Approved by FDA

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IP/DIC/BX/16 2/04

**IDEXX**  
LABORATORIES

**SURPASS™**  
(1% diclofenac sodium)



**SURPASS™**  
(1% diclofenac sodium)

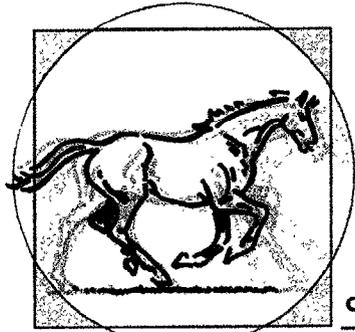
Topical Anti-Inflammatory Cream for Use in Horses

Net wt. 124 grams

**IDEXX**  
LABORATORIES



**SURPASS™**  
(1% diclofenac sodium)

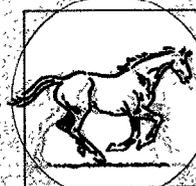


**SURPASS™**  
(1% diclofenac sodium)

Topical Anti-Inflammatory Cream for Use in Horses

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

Net wt. 124 grams



**SURPASS™**  
(1% diclofenac sodium)

Topical Anti-Inflammatory Cream for Use in Horses

Net wt. 124 grams

**IDEXX**  
LABORATORIES

DISPLAY CARTON

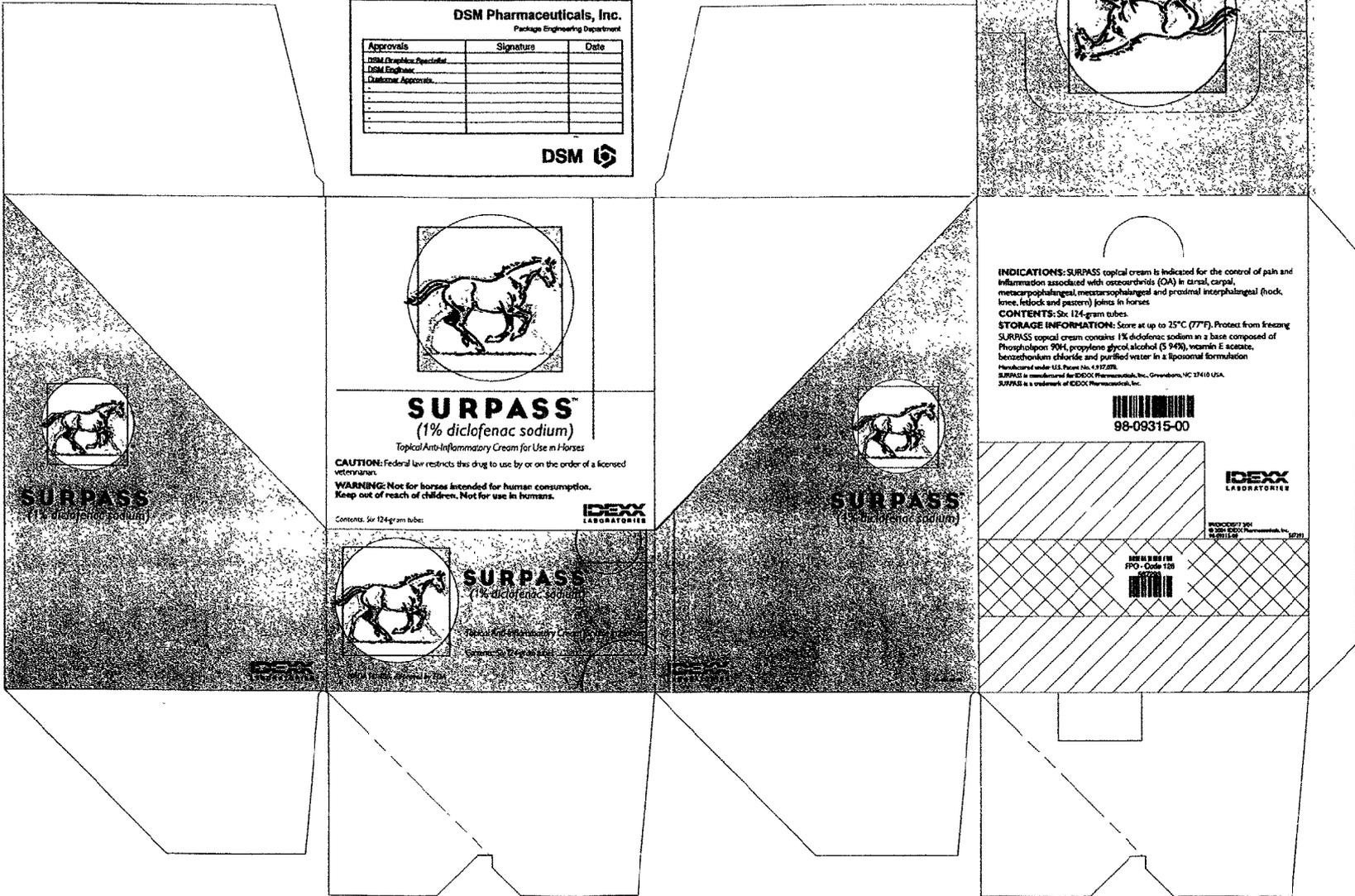
567293  
 Display Box - Surpass Cream 4.0 oz.  
 Size: 5-1/8" x 5-1/16" x 7-21/32"



**DSM Pharmaceuticals, Inc.**  
 Package Engineering Department

| Approvals               | Signature | Date |
|-------------------------|-----------|------|
| DSM Graphics Specialist |           |      |
| DSM Engineer            |           |      |
| Customer Approvals      |           |      |
|                         |           |      |
|                         |           |      |
|                         |           |      |
|                         |           |      |

**DSM**

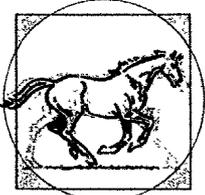


**DSM Pharmaceuticals, Inc.**

Package Engineering Department

| Approvals               | Signature | Date |
|-------------------------|-----------|------|
| DSM Graphics Specialist |           |      |
| DSM Engineer            |           |      |
| Customer Approvals      |           |      |
|                         |           |      |
|                         |           |      |
|                         |           |      |
|                         |           |      |

**DSM**



**SURPASS**<sup>™</sup>  
 (1% diclofenac sodium)

Topical Anti-Inflammatory Cream for Use in Horses

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

**WARNING:** Not for horses intended for human consumption. Keep out of reach of children. Not for use in humans.

Contents: Six 124-gram tubes.

**DEX**  
 LABORATORIES



**SURPASS**<sup>™</sup>  
 (1% diclofenac sodium)

Topical Anti-Inflammatory Cream for Use in Horses

Surpass is a registered trademark of DSM Pharmaceuticals, Inc.

**SURPASS**<sup>™</sup>  
 (1% diclofenac sodium)



**INDICATIONS:** SURPASS topical cream 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.

**CONTENTS:** Six 124-gram tubes.

**STORAGE INFORMATION:** Store at up to 25°C (77°F). Protect from freezing. SURPASS topical cream contains 1% diclofenac sodium in a base composed of Phospholipon 90H, propylene glycol alcohol (S 94X), vitamin E acetate, benzethonium chloride and purified water in a liposomal formulation.

Manufactured under U.S. Patent Nos. 4,972,878.  
 SURPASS is manufactured for DSM Pharmaceuticals, Inc., Greensboro, NC 27410 USA.  
 SURPASS is a trademark of DSM Pharmaceuticals, Inc.



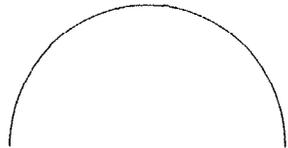
98-09315-00

**DEX**  
 LABORATORIES

PROCESSED BY  
 DSM Pharmaceuticals, Inc.  
 10/2011



98-09315-00



**INDICATIONS:** SURPASS topical cream 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.

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Manufactured under U.S. Patent No. 4,937,078.

SURPASS is manufactured for IDEXX Pharmaceuticals, Inc., Greensboro, NC 27410 USA.

SURPASS is a trademark of IDEXX Pharmaceuticals, Inc.



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**IDEXX**  
LABORATORIES

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