

Banamine® Transdermal Technical Bulletin

Clinical efficacy of a novel Flunixin Transdermal formulation for the control of pyrexia associated with naturally occurring bovine respiratory disease: a multicenter field trial

Background

Banamine® Transdermal (flunixin transdermal solution) is a new pour-on formulation containing flunixin meglumine (50 mg/mL) intended for use in cattle at a dose rate of 3.3 mg/kg BW (1 mL/33 lbs. BW).

Objective

The objective of this prospective, randomized, masked study was to demonstrate the effectiveness and safety of Banamine Transdermal in cattle suffering from fever associated with naturally occurring bovine respiratory disease (BRD).

Materials and Methods

This multicenter field study was conducted in four states (Kansas, Texas, Nebraska and California). Calves acquired from auction markets arrived at study sites, were identified with ear tags, weighed and vaccinated against viral and clostridial pathogens.

Enrollment criteria for BRD required that each animal have all of the following:

- A respiratory score of 2 or 3
- An attitude score of 2 or 3 (Table 1)
- A rectal temperature of ≥ 104.5 degrees F

RESPIRATORY SCORE		
SCORE	IDENTIFICATION	DESCRIPTION
0	Normal	No abnormal respiratory symptoms. Rate and effort are appropriate for the environment.
1	Mild respiratory distress	Serous nasal or ocular discharge and/or cough.
2	Moderate respiratory distress	Mucous or mucopurulent nasal or ocular discharge and/or increase in respiratory rate or effort.
3	Severe respiratory distress	Marked increase in respiratory rate or effort, with one or more of the following: open mouth breathing, abdominal breathing, and/or extended head.

ATTITUDE SCORE

SCORE	IDENTIFICATION	DESCRIPTION
0	Normal	Bright, alert, responsive.
1	Mildly depressed	May stand isolated with head down, ears drooping, but responsive to stimulation.
2	Moderately depressed	May remain recumbent or stand isolated with head down, may show signs of muscle weakness (standing cross-legged, knuckling or swaying when walking), depression obvious when stimulated.
3	Severely depressed	May be recumbent and reluctant to rise, or if standing is isolated and reluctant to move. When moving, ataxia, knuckling or swaying evident. Head carried low with ears drooping. Eyes dull, possible excess salivation/lacrimation, obvious gauntness.
4	Moribund	Unable to stand; approaching death; highly unlikely to respond to antimicrobial therapy.

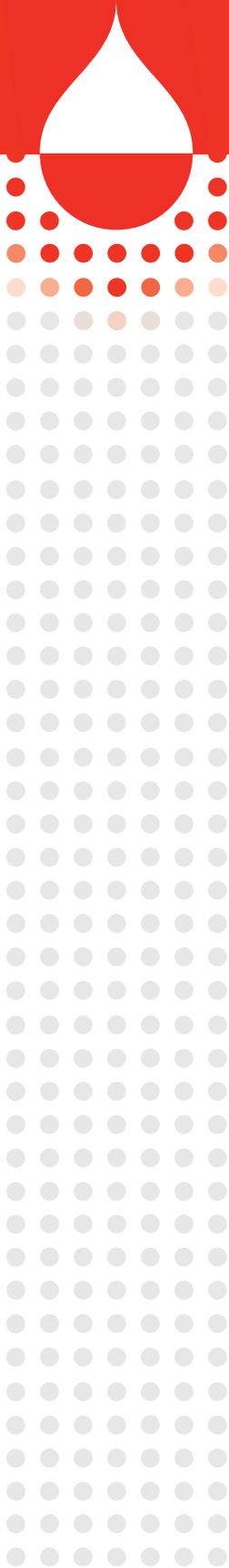
Table 1. Respiratory and attitude scores.

A randomized complete block design was used at each location. Qualifying animals were weighed and received either Banamine Transdermal at 3.33 mg/kg or placebo at 1 mL/15 kg administered topically along the dorsal midline from withers to tail head. No antimicrobials were administered.

At 6 hours ± 45 minutes after dosing (H+6), rectal temperature was measured and the dosing site was examined. Calves were off the study after the H+6 observations.

Treatment success rate was analyzed by a generalized linear mixed model where a binomial distribution was assumed and a logit link was used. Treatment, sex and treatment by sex interactions were included as fixed effects. Site, study pen nested in site by sex, and site by sex by treatment interaction and the residual term were included in the model as random effects.

The contrast between the treatment success rates of the 3.3 mg/kg flunixin transdermal solution-treated group and the control group was evaluated at the two-sided 0.05 significance level.



An animal was designated as a treatment success when the rectal temperature decreased by ≥ 2 degrees F from the inclusion rectal temperature at six hours (+/- 45 minutes) post-treatment.

Results

During the study period across the four study sites, environmental temperatures ranged from 30 degrees F to 94 degrees F.

A total of 251 purebred or crossbred calves (156 males, 95 females), predominantly Angus, Charolais, Hereford, and Simmental, with body weights ranging from 224 to 620 pounds, were enrolled into the study across the four sites (Table 2).

There were 16 animals removed from the statistical analysis because they were exposed to hide-wetting moisture between the time of treatment and the final rectal temperature measurements.

Study Site	Treatment Group	Animals Enrolled	Age (months)	Weight (pounds)	Breed
Kansas	Control	24	6-10	410-553	Angus, Charolais, Hereford, other
	Banamine Transdermal	24			
Texas	Control	40	6-8	388-557	Angus, Charolais, Hereford, Simmental, other
	Banamine Transdermal	41			
Nebraska	Control	30	6-8	337-619	Angus, Charolais, Simmental, other
	Banamine Transdermal	30			
California	Control	29	6	224-500	Angus, Charolais, Hereford, Simmental
	Banamine Transdermal	33			

Table 2. Number of animal enrolled with BRD and corresponding age, weight and type of breed of calves receiving flunixin transdermal (3.3 mg/kg BW flunixin) control (placebo) at four sites.

Rectal temperatures at enrollment ranged from 104.54 degrees F to 107.78 degrees F. The overall mean (\pm SD) temperature decrease was 1.3 (\pm 0.6) degrees F in the flunixin transdermal-treated group and 0.2 (\pm 0.6) degree F in the control group ($P < 0.0001$) (Table 3, Figure 1 and Figure 2).

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Study Site	BANAMINE TRANSDERMAL GROUP					
	Temperature at enrollment (°F)		Temperature 6 hours post-administration (°F)		Decrease (°F)	
	Mean	Mean	Mean	Std Dev.	Min	Max
Kansas	105.26	102.02	1.8	0.6	0.7	3.2
Texas	105.26	103.28	1.1	0.5	(0.1)	2.2
Nebraska	104.9	102.2	1.5	0.4	0.9	2.8
California	105.26	103.46	1.0	0.5	—	2.1
Total	105.26	102.92	1.3	0.6	(0.1)	3.2

Study Site	CONTROL (PLACEBO) GROUP					
	Temperature at enrollment (°F)		Temperature 6 hours post-administration (°F)		Decrease (°F)	
	Mean	Mean	Mean	Std Dev.	Min	Max
Kansas	105.26	104.72	0.3	0.5	(0.6)	1.4
Texas	105.08	105.08	(0.0)	0.7	(1.9)	0.9
Nebraska	105.08	104.18	0.4	0.7	(0.7)	2.4
California	105.08	104.9	0.2	0.5	(0.7)	0.9
Total	105.08	104.72	0.2	0.6	(1.9)	2.4

Table 3. Mean rectal temperature of cattle enrolled with BRD and at six hours after administration of flunixin transdermal (3.3 mg/kg BW flunixin) or control (placebo) and corresponding mean, standard deviation, minimum and maximum of the mean decrease in rectal temperature.

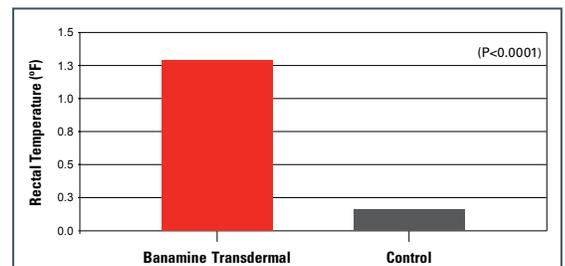


Figure 1. Mean rectal temperature decrease of cattle enrolled with BRD after six hours of administration of flunixin transdermal (3.3 mg/kg BW flunixin) or control.

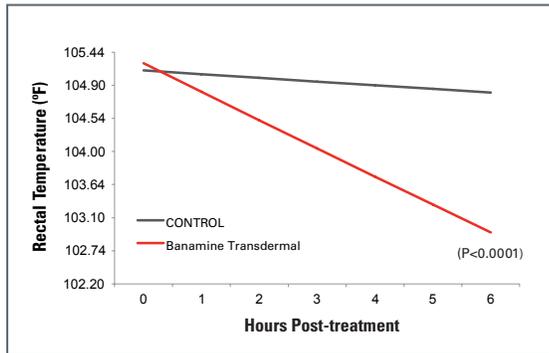
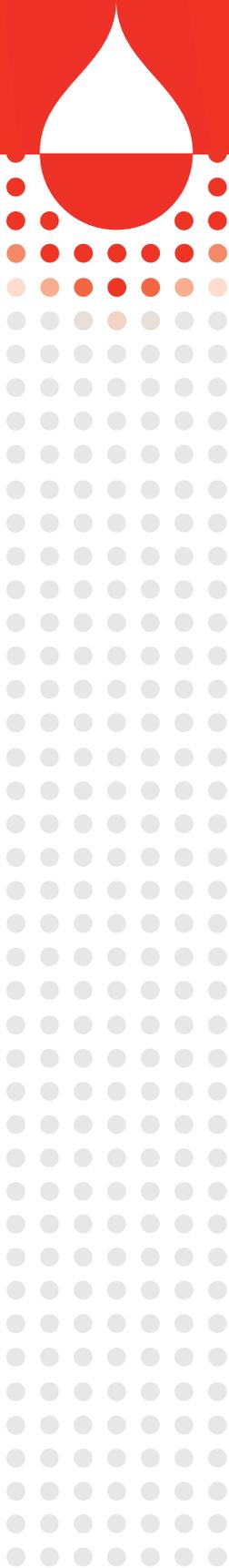


Figure 2. Mean rectal temperature at enrollment and at six hours post-treatment of cattle enrolled with BRD and receiving either flunixin transdermal (3.3 mg/kg BW flunixin) or control.

The proportion of calves with a minimum 1 degree F temperature decrease was 90 percent in the Banamine Transdermal-treated group and 24.3 percent in the control group ($P < 0.0001$) (Figure 2). The proportion of calves with at least 2 degrees F temperature decrease was 58.3 percent in the Banamine Transdermal-treated group and 6.1 percent in the control group ($P < 0.001$). All 251 enrolled calves were observed at H+6 for abnormalities at the dosing site. No abnormalities were reported at the dosing site in the treated animals.

Conclusions

This study demonstrates that Banamine Transdermal is safe and effective for the control of pyrexia associated with naturally occurring BRD in a variety of cattle in a broad range of environmental conditions.

IMPORTANT SAFETY INFORMATION: NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN. Only for topical use in beef and dairy cattle. Do not use Banamine Transdermal pour-on within 48 hours of expected parturition. Do not use in animals showing hypersensitivity to flunixin meglumine. Cattle must not be slaughtered for human consumption within 8 days of the last treatment. Not for use in female dairy cattle 20 months of age or older, including dry dairy cows; use in these cattle may cause drug residues in milk and/or in calves born to these cows or heifers. Not for use in suckling beef calves, dairy calves, and veal calves. A withdrawal period has not been established for this product in pre-ruminating calves. Not for use in dairy or beef bulls intended for breeding because reproductive safety has not been evaluated.

Banamine®
Transdermal

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Product Information
NADA #141-450, Approved by FDA

Banamine® Transdermal

(flunixin transdermal solution)

Pour-On for Beef and Dairy Cattle
50 mg/mL

Non-Steroidal Anti-inflammatory Drug

Only for topical use in beef and dairy cattle. Not for use in beef bulls intended for breeding; dairy bulls; female dairy cattle 20 months of age or older, including dry dairy cows; and suckling beef calves, dairy calves, and veal calves.

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

DESCRIPTION: Each milliliter of Banamine Transdermal pour-on contains 50 mg flunixin (equivalent to 83 mg flunixin meglumine), 150 mg pyrrolidone, 50 mg L-menthol, 500 mg propylene glycol dicaprylate/dicaprate NF, 0.20 mg FD&C Red No. 40, and glycerol monocaprylate NF qs.

INDICATIONS: Banamine Transdermal pour-on is indicated for the control of pyrexia associated with bovine respiratory disease and the control of pain associated with foot rot in steers, beef heifers, beef cows, beef bulls intended for slaughter, and replacement dairy heifers under 20 months of age.

DOSEAGE AND ADMINISTRATION: Apply only once at a dose of 3.3 mg flunixin per kg body weight (1.5 mg/lb; 3 mL per 100 lbs) typically in a narrow strip along the dorsal midline from the withers to the tailhead. Round all doses up to the nearest weight increment on the dosing chamber. Do not treat cattle if the hide is wet or to be nearest wet in the six hours after dosing because effectiveness has not been evaluated under wet hide conditions.

Practice the Administration and Overfill Reduction Instructions a few times to become familiar with operating the package before dosing animals.

Step 1

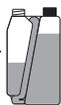
On first use remove cap and peelable seal from the dosing chamber. Do not remove cap from the bottle.



If the dosing chamber is overfilled, follow the Overfill Reduction Instructions.

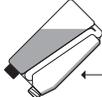
Step 2

Hold the bottle upright and at eye level while slowly and gently squeezing the bottle to fill the dosing chamber to the selected mark.



Step 3

Pour the measured volume on the dorsal midline from withers to tail head. Application to a small area should be avoided.

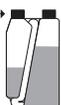


A small amount of liquid will remain on the walls of the chamber, but the chamber is calibrated to account for this.

OVERFILL REDUCTION INSTRUCTIONS

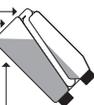
Step 1

Re-apply cap to dosing chamber and tighten. Confirm the cap is tight.



Step 2

Transfer Tube Air Pocket



Tilt the bottle to allow an air pocket form at the beginning of the transfer tube inside the bottle.

Step 3

Hold the bottle horizontally to allow product to cover the end of the transfer tube inside the dosing chamber.



Step 4

Squeeze and release the bottle repeatedly. Product will return to the bottle through the transfer tube.

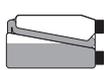
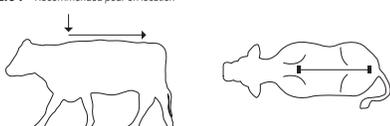


Figure 1 – Recommended pour-on location



CONTRAINDICATIONS: NSAIDs inhibit production of prostaglandins which are important in signaling the initiation of parturition. The use of flunixin can delay parturition and prolong labor which may increase the risk of stillbirth. Do not use in animals showing hypersensitivity to flunixin meglumine.

USER SAFETY WARNINGS: Not for use in humans. Keep out of reach of children. Flunixin transdermal solution is a potent non-steroidal anti-inflammatory drug (NSAID), and ingestion may cause gastrointestinal irritation and bleeding, kidney, and central nervous system effects.

This product has been shown to cause severe and potentially irreversible eye damage (conjunctivitis, iritis, and corneal opacity) and irritation to skin in laboratory animals. Users should wear suitable eye protection (face shields, safety glasses, or goggles) to prevent eye contact, and chemical-resistant gloves and appropriate clothing (such as long-sleeve shirt and pants) to prevent skin contact and/or drug absorption. Wash hands after use.

In case of accidental eye contact, flush eyes immediately with water and seek medical attention. If wearing contact lenses, flush eyes immediately with water before removing lenses. **In case of accidental skin contact and/or clothing contamination, wash skin thoroughly with soap and water and launder clothing with detergent. In case of ingestion do not induce vomiting and seek medical attention immediately.** Probable mucosal damage may contraindicate the use of gastric lavage. Provide product label and/or package insert to medical personnel.

RESIDUE WARNINGS: Cattle must not be slaughtered for human consumption within 8 days of the last treatment. Not for use in female dairy cattle 20 months of age or older, including dry dairy cows; use in these cattle may cause drug residues in milk and/or in calves born to these cows or heifers. Not for use in suckling beef calves, dairy calves, and veal calves. A withdrawal period has not been established for this product in pre-ruminating calves.

PRECAUTIONS: As a class, cyclo-oxygenase inhibitory NSAIDs may be associated with gastrointestinal, renal, and hepatic toxicity. Sensitivity to drug-associated adverse events varies with the individual patient. Patients at greatest risk for adverse events are those that are dehydrated, on concomitant diuretic therapy, or those with renal, cardiovascular, and/or hepatic dysfunction. Banamine transdermal should be used with caution in animals with suspected pre-existing gastric erosions or ulcerations. Concurrent administration of other NSAIDs, corticosteroids, or potentially nephrotoxic drugs should be avoided or used only with careful monitoring because of the potential increase of adverse events.

NSAIDs are known to have potential effects on both parturition (see Contraindications) and the estrous cycle. There may be a delay in the onset of estrus if flunixin is administered during the prostaglandin phase of the estrous cycle. NSAIDs are known to have the potential to delay parturition through a toxic effect. The use of NSAIDs in the immediate postpartum period may interfere with uterine involution and expulsion of fetal membranes. Cows should be monitored carefully for placental retention and metritis if Banamine Transdermal pour-on is used within 24 hours after parturition.

Not for use in dairy or beef bulls intended for breeding because reproductive safety has not been evaluated.

CLINICAL PHARMACOLOGY: Flunixin meglumine is a non-steroidal, anti-inflammatory drug. It is a weak acid (pKa=5.82) which exhibits a high degree of plasma protein binding (approximately 99%).² However, free (unbound) drug appears to readily partition into body tissues (Vss predictions range from 297 to 782 mL/kg).^{2,3} In cattle, elimination occurs primarily through biliary excretion.

Flunixin persists in inflammatory tissues⁴ and is associated with anti-inflammatory properties which extend well beyond the period associated with detectable plasma drug concentrations.⁴ Therefore, prediction of drug concentrations based upon the estimated plasma terminal elimination half-life will likely underestimate both the duration of drug action and the concentration of drug remaining at the site of activity.

Pharmacokinetic properties of flunixin transdermal solution in cattle administered at a dose of 2.5 mg/kg, are summarized in Table 1, comparing results between animals that were allowed to self- and allo-lick vs. animals that were prevented from licking. Animals that were allowed to self- or allo-lick had lower rate and extent of absorption when compared to the animals prevented from licking. However, no dose adjustment is needed to account for the effect of licking because the substantial evidence of effectiveness was demonstrated in animals that were allowed to lick.

Table 1. Average (+/- standard deviation [SD]) PK parameters after a single administration of flunixin transdermal solution at a dose of 2.5 mg/kg in cattle that were either allowed to lick or prevented from allo- and self-licking (n = 24/group).

PK parameter	Non-licking		Licking	
	Mean	±SD	Mean	±SD
C _{max} (ng/mL)	1496	769	N/A	N/A
Concentration at 2 h*	1282	533	1072	353
T _{max} (h)	1.29	0.464	N/A	N/A
AUC _{0-24h} (ng* h/mL)	7499	2131	6827	4672
T _{1/2} (h)	8	2	9	6

* First blood level in the licking group was taken at 2 hours post-dose.

First blood sample in non-licking group was taken at 0.25 hours post-dose.

C_{max}: Maximum observed plasma concentration

T_{max}: Time at which C_{max} was observed

AUC_{0-24h}: Area under the plasma concentration versus time curve measured between 2 hours and the time of the last quantifiable concentration

T_{1/2}: Terminal elimination half-life

Absorption of flunixin transdermal solution in cattle is dependent on environmental temperature. The effect of temperature on flunixin absorption was tested in temperatures ranging from 15.3 to 20.1 °F (average low in the coldest study) to 80 to 100 °F (average high in the warmest study). Flunixin concentrations were consistently lower when the pour-on product was administered in a cold (temperature) rather than hot (temperature) environment. However, the clinical effectiveness was demonstrated over the range of environmental conditions expected under field conditions. No dose adjustments are necessary due to environmental temperature.

References:

- Johansson M, Anler EL. Gas chromatographic analysis of flunixin in equine urine after extractive methylation. *J Chromatogr.* 1988; 427:55-66.
- Odensvik K, Johansson M. High-performance liquid chromatography method for determination of flunixin in bovine plasma and pharmacokinetics after single and repeated doses of the drug. *Am J Vet Res.* 1995; 56:489-495.
- Anderson KL, Neff-Davis CA, Davis LE, Bass VD. Pharmacokinetics of flunixin meglumine in lactating cattle after single and multiple intramuscular and intravenous administrations. *Am J Vet Res.* 1990; 51:1464-1467.
- Odensvik K. Pharmacokinetics of flunixin and its effect on prostaglandin F₂ metabolite concentrations after oral and intravenous administration in heifers. *J Vet Pharmacol Ther.* 1995; 18:254-259.
- Hardee GE, Smith JA, Harris SJ. Pharmacokinetics of flunixin meglumine in the cow. *Res Vet Sci.* 1985; 39:110-112.
- Lees P, Higgins AJ. Flunixin inhibits prostaglandin E₂ production in equine inflammation. *Res Vet Sci.* 1984; 37:347-349.

TARGET ANIMAL SAFETY: In a target animal safety study in 32 six-month old beef cattle (16 castrated males and 16 females), flunixin transdermal solution was administered topically at 3.3, 9.9, and 16.5 mg/kg body weight (1X, 3X, and 5X the labeled dose) on Days 1, 2, and 3 (3X the labeled administration frequency). Cattle were continuously restrained to prevent licking. In addition, the study was conducted under warm environmental conditions (70 °F to 80 °F on dosing days). One animal in the 3X group and three animals in the 5X group exhibiting twisting, kicking, rubbing on the fence, and/or prancing, starting 5 to 15 minutes after dosing and lasting up to an hour after dosing on both Days 2 and 3. Two 5X animals had positive fecal occult blood on one of three post-treatment days, and one 5X animal had positive fecal occult blood on Days 2 and 3 post-treatment. Trace occult blood was found in the urine of three animals: one 5X animal on Day 1, one 5X animal on Day 3, and one 3X animal on Day 3. Test article-related pathology changes included a dose-related increase in the incidence and severity of abomasal erosions and ulcerations, and inflammatory cell infiltrates, epidermal necrosis, and small areas of demal necrosis at the application site. The abomasal lesions correlated with fecal occult blood in three 5X animals. There were no animals with any other evidence of gastrointestinal bleeding or clinical signs of abomasal ulceration during the study.

Application site reactions, including dandruff/skin flakes, hair damage (thin, broken, brittle hair), and skin thickening were observed in effectiveness and/or supportive studies. The application site reactions were first observed around three to seven days post-dosing and lasted for about 14 days. These reactions were cosmetic in nature and generally resolved without treatment.

A pharmacokinetic evaluation demonstrated that the systemic exposure of flunixin is markedly lower when administered transdermally at a dose of 3.3 mg flunixin/kg BW than when administered intravenously at a dose of 2.2 mg flunixin/kg BW, therefore, female reproductive safety is supported by reproductive safety studies conducted for the approval of BANAMINE (flunixin meglumine injection) in cattle, NADA 101-479.

EFFECTIVENESS: Pharmacokinetic studies established that the absorption of flunixin administered transdermally to cattle is highly dependent on environmental temperature. Therefore the effectiveness of flunixin transdermal solution for the control of pyrexia associated with bovine respiratory disease was demonstrated under a range of environmental temperatures in two studies: a field study conducted at four geographic locations (California, Kansas, Nebraska, and Texas) under moderate environmental temperatures (average temperatures ranged from 42 °F to 74 °F on enrollment days) and a field study conducted at a single site (Nebraska) under cold environmental conditions (average temperatures ranged from 2 °F to 20 °F on enrollment days). In both studies, cattle were housed in groups and were not prevented from licking.

In both studies, cattle exhibiting clinical signs of BRD and having a rectal temperature of at least 104.5 °F were enrolled. A total of 235 cattle in the multi-location field study and 50 cattle at the single site field study were administered either flunixin transdermal solution (3.3 mg/kg BW) or an equivalent volume of dyed saline as a pour-on once on Day 0. Six hours after treatment, rectal temperatures were measured. The treatment success rate of the flunixin transdermal solution-treated group was compared to the treatment success rate in the dyed saline-treated group. A treatment success was defined as a drop in rectal temperature of 2 °F in an individual animal. In the multi-location study, the treatment success rate was significantly different (p < 0.0001) and higher for the flunixin transdermal solution-treated group (70/120, 58.3%) compared to the dyed saline-treated control group (7/115, 6.1%). In the single site study, the treatment success rate was significantly different (p = 0.0002) and higher for the flunixin transdermal solution-treated group (19/25, 76%) compared to the dyed saline-treated control group (4/25, 16%).

The effectiveness of flunixin transdermal solution for the control of pain associated with foot rot in beef and dairy cattle was demonstrated under a range of environmental temperatures in two studies: an induced infection model study conducted in Nebraska with temperatures ranging from 61 °F to 85 °F on the day of enrollment and treatment; and an induced infection model study conducted in Kansas with temperatures ranging from 27 °F to 53 °F on the day of enrollment and treatment. In both studies, cattle from both treatment groups were commingled in pens and were not prevented from licking.

In each study, cattle were challenged by subcutaneous injection of a culture of *Fusobacterium necrophorum* into the interdigital space of the right front foot using a method that was validated to induce pain representative of foot rot. Cattle were enrolled when they demonstrated signs of pain associated with foot rot based on lameness, interdigital lesion, and interdigital swelling criteria. Pressure mat gait parameters maximum total force (kgf) and contact area (cm²) were also measured at enrollment. A total of 30 cattle at each site were administered either flunixin transdermal solution (3.3 mg/kg BW) or an equivalent volume of dyed saline as a pour-on once on Day 0. Six hours after treatment, lameness scores and pressure mat gait parameters maximum total force and contact area were measured.

Effectiveness was determined independently at each site based on treatment success rates at six hours after treatment; and the change in maximum total force and contact area between enrollment and six hours after treatment. A treatment success was defined as a decrease in lameness score by ≥1 (scale 1 to 5, with enrollment of animals with lameness score ≥3) from the enrollment lameness score. The treatment success rate of the flunixin transdermal solution-treated group was compared to the treatment success rate in the dyed saline-treated group at both sites.

Changes in biometric gait parameters were also compared between the treatment groups.

In the Nebraska study, the treatment success rate was significantly different and higher for the flunixin transdermal solution-treated group (15/15, 100%) compared to the dyed saline-treated group (1/15, 6.67%), and the mean change in maximum total force and mean change in contact area were statistically significantly different (p < 0.0001) and higher in the flunixin transdermal solution-treated group (43.08 kgf and 16.76 cm²) compared to the dyed saline-treated control group (4.14 kgf and 2.70 cm²). In the Kansas study, the treatment success rate was significantly different (p = 0.0367) and higher for the flunixin transdermal solution-treated group (14/15, 93.33%) compared to the dyed saline-treated group (8/15, 53.33%), and the mean change in maximum total force and mean change in contact area were statistically significantly different (p = 0.0002 and p < 0.0001, respectively) and higher in the flunixin transdermal solution-treated group (34.32 kgf and 16.38 cm²) compared to the dyed saline-treated control group (-0.54 kgf and -0.96 cm²).

CONTACT INFORMATION: For technical assistance or to report a suspected adverse drug experience, call: 1-800-219-9286. For customer service or to request a Safety Data Sheet (SDS), call: 1-800-211-3573. For additional Banamine Transdermal pour-on information go to www.BanamineD.com. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at <http://www.fda.gov/AnimalVeterinary/SafetyHealth>.

HOW SUPPLIED: Banamine Transdermal pour-on, is available in 100-mL (NDC 0061-4363-01), 250-mL (NDC 0061-4363-02), and 1-L (NDC 0061-4363-03) bottles.

STORAGE INFORMATION: Store at or below 30 °C (86 °F). Use within 6 months of first opening.

For Patent information: <http://www.merck.com/product/patent/home.html>. NADA 141-450, Approved by FDA. Use Only as Directed. Copyright ©2018, Intervet Inc., a subsidiary of Merck & Co. All rights reserved. Made in Germany. Distributed by: Intervet Inc. d/b/a Merck Animal Health, Madison, NJ 07940

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