Introducing Banamine® Transdermal. Finally, the ease and convenience of a pour-on.

Banamine®
Transdermal
(flunixin transdermal solution)

MERCK
Animal Health

BANAMINE TRANSDERMAL INDICATIONS:

- For the control of pyrexia associated with BRD
- For the control of pain associated with foot rot

New approach improves animal well-being

Using pour-on application to reduce fever in cattle caused by BRD or pain due to foot rot is in alignment with industry efforts to continuously improve animal care and mitigate pain. It is the newest example of Merck Animal Health's commitment to improve animal care and animal caregiver options through innovation.

Visit **BanamineTD.com** for more information.

THE FIRST AND ONLY POUR-ON FOR RELIEF OF PAIN AND FEVER

Pain and fever can cause cattle to go off feed. But new, easy-to-use Banamine® Transdermal (flunixin transdermal solution) helps get 'em back where they belong.

FDA-approved to control pain due to foot rot and fever due to BRD, Banamine Transdermal is the only non-steroidal anti-inflammatory (NSAID) cattle product available with a convenient pour-on route of administration.

Uniquely designed to go to work quickly

Banamine Transdermal controls pain and fever quickly. Studies show that a single dose is absorbed into the bloodstream within minutes* and has long duration of activity at the site of inflammation**, giving cattle the best opportunity to be healthy and productive.

Easy to dose

The pre-calibrated packaging helps ensure the right dose is given every time. The unique bottle design allows for proper topical application along the animal's back. The red-colored solution makes it simple to accurately and quickly measure the dose volume for each animal.

*Data on file: EX-05331-00

**Lees P, Higgins AJ. Flunixin inhibits prostaglandin E2 production in equine inflammation. *Res Vet Sci.* 1984; 37:347-349.

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.

Easy to apply

Patented delivery eliminates the need for IV administration, so you can make quick work of treatment with this simple pour-on. Its needle-free and efficient administration means there is less labor and supplies than what is associated with injectable administration. The result is a decreased cost per treatment, due to the reduction in time spent treating animals.

Easy on animals

Transdermal application requires less handling, resulting in less stress on the animals. Managing fever and pain is important to a sick animal's recovery, and Banamine Transdermal is specially formulated to rapidly absorb into the bloodstream. Reducing stress through easy application and quick relief leads to inherent health and growth advantages. Plus, with needle-free, transdermal administration, there is no risk of injection site lesions.

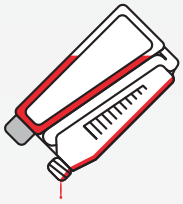
DOSING AND ADMINISTRATION MADE EASY

Four simple steps for this new route of administration

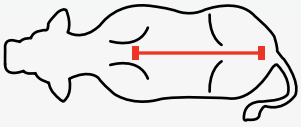
Step 1: Determine the animal's body weight and select the correct dose using the bottle's dosing chamber, which is calibrated in pounds of body weight. Banamine Transdermal is labeled to be administered once at a dose of 3 mL per 100 pounds on dry skin.

Step 2: On first use, remove the cap and peelable seal from the dosing chamber. Do not remove the cap from the storage bottle.

Step 3: 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 4: Pour the measured volume on the midline of the animal's back extending from the withers to tail head. Localized application to smaller areas should be avoided.



Users should wear eye protection, such as safety glasses or goggles, to prevent eye contact. Chemical-resistant gloves and appropriate clothing, such as a long-sleeved shirt and pants, should be worn to prevent skin contact and/or drug absorption. Wash hands after use.

FREQUENTLY ASKED QUESTIONS ABOUT ADMINISTERING BANAMINE TRANSDERMAL

How long should animals be protected from rain exposure after treatment?

Six hours.

What is the meat withdrawal?

Eight days.

Should the dose be adjusted based on air temperatures?

There is no need to adjust the dose. While studies demonstrated peak plasma flunixin concentrations were consistently lower when the pour-on product was administered in cold temperatures vs. hot temperatures, the bioavailability is the same. Clinical effectiveness was demonstrated over a range of environmental temperatures expected under field conditions.

Is there concern over animals licking Banamine Transdermal from treated animals?

No. A study where animals were allowed to self-lick or lick pen mates demonstrated a 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 substantial evidence of effectiveness was demonstrated in animals that were allowed to lick.

PROOF FROM THE FIELD

Safe and efficacious relief of pain and fever

Results from field trials demonstrate that Banamine Transdermal can be an important part of a BRD or foot rot treatment protocol.

TRIALS SUMMARY FOR BRD RELIEF

- Successfully and safely controlled fever as indicated by the significant decrease in rectal temperature

TRIALS SUMMARY FOR LAMENESS RELIEF

- Successfully and safely reduced pain due to foot rot
- Demonstrated to statistically lower lameness and lesion scores

CONTROL FEVER ASSOCIATED WITH BRD

Banamine Transdermal was determined to be safe and efficacious in controlling fever associated with BRD.

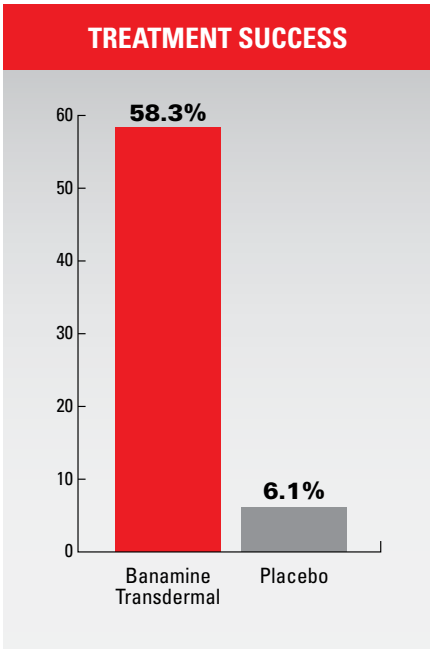
Trial setup

Field studies were conducted in four states with 251 total animals enrolled and diagnosed with BRD. At enrollment, rectal temperatures ranged from 104.5 to 107.8°F. Animals received either 3 mL per 100 pounds of Banamine Transdermal or a placebo. No antimicrobials were administered.

Six hours after treatment, rectal temperature was measured and treatment sites were observed for abnormalities. An animal was considered a treatment success if rectal temperature was reduced by ≥2°F.

Results

Treatment success was 58.3 percent for animals receiving Banamine Transdermal compared with 6.1 percent for the placebo group ($p<0.001$). Treatment sites were considered normal in animals treated with Banamine Transdermal.



CONTROL PAIN ASSOCIATED WITH FOOT ROT

Banamine Transdermal was determined to be safe and efficacious in controlling pain associated with foot rot.

Trial setup

Field studies were conducted in two states with 30 steers enrolled weighing between 717 and 1,085 pounds. Animals were experimentally induced with foot rot infection in the right front limb. After 48 hours, animals were given either Banamine Transdermal (3 mL per 100 pounds) or placebo (dyed saline). No antimicrobials were administered.

At the time of treatment and six hours after treatment, lameness scores and pressure mat gait parameters of both maximum total force and contact area were measured. An animal was considered a treatment success if the lameness score decreased by more or equal to one point.

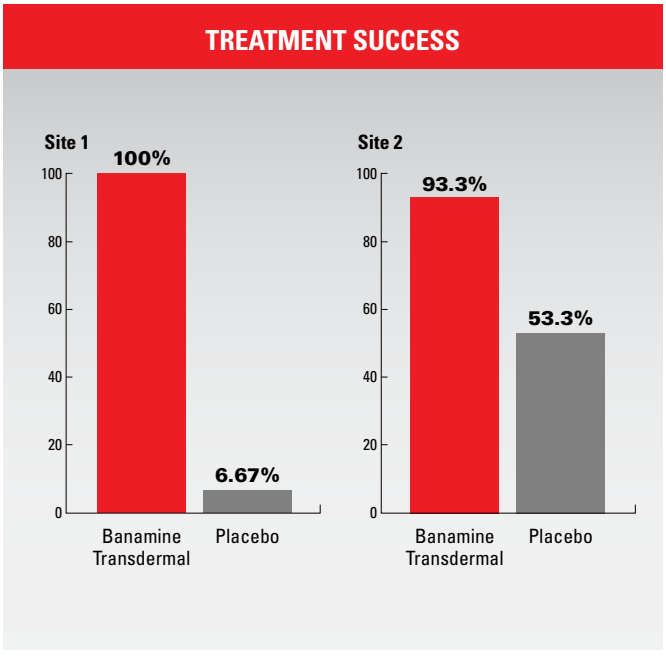
Results

At site 1, lameness score treatment success was 100 percent and significantly different for animals receiving Banamine Transdermal. This compares with 6.67 percent for the placebo group. The mean change in maximum total force and mean change in contact area were significantly different ($p<0.0001$) and higher in the flunixin transdermal solution-treated group compared to the placebo group.

At site 2, the lameness score treatment success rate was 93.3 percent and significantly different for the animals given Banamine Transdermal. This compares with 53.3 percent for the placebo group. The mean change in maximum total force and mean change in contact area were significantly different ($p= 0.0002$ and $p<0.0001$, respectively) and higher in the flunixin transdermal solution-treated group compared to the placebo group.

The marked increases in both maximum total force and total contact area at both study sites were clinically interpreted as animals able to plant their affected foot in a more normal fashion and bear more weight on the affected limb, supporting clinical improvement in lameness as a result of less pain.

While the cause of lameness should always be treated, this study demonstrated Banamine Transdermal significantly reduced lameness, which is an expression of pain.



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.

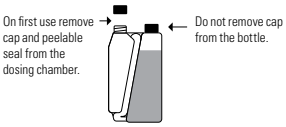
DESCRIPTION: Each milliliter of Banamine Transdermal pour-on contains 50 mg flunixin (equivalent to 83 mg flunixin meglumine), 150 mg pyrrolidone, 50 mg L-menthol, 500 mg propylene glycol dicaprylate/dicaprate NF, 0.20 mg FD&C Red No. 40, and glycerol monocaprylate NF qs.

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.

DOSAGE 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) topically 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 may get wet in the six hours after dosing because effectiveness has not been evaluated under wet hide conditions.

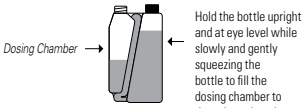
Practice the Administration and Overfill Reduction Instructions a few times to become familiar with operating the package before dosing animals.

Step 1

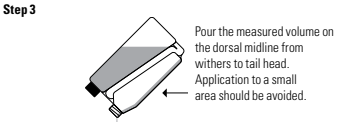


If the dosing chamber is overfilled, follow the Overfill Reduction Instructions.

Step 2



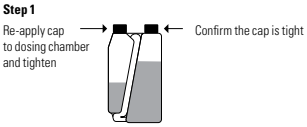
Step 3



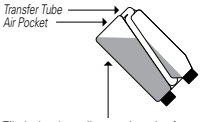
A small amount of liquid will remain on the walls of the chamber, but the chamber is calibrated to account for this.

OVERFILL REDUCTION INSTRUCTIONS

Step 1

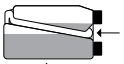


Step 2



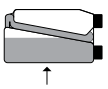
Tilt the bottle to allow an air pocket form at the beginning of the transfer tube inside the bottle.

Step 3



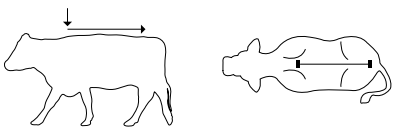
Hold the bottle horizontally to allow product to cover the end of the transfer tube inside the dosing chamber

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 Banamine Transdermal pour-on within 48 hours of expected parturition. 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 tocolytic 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)[1] 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).[2,5] In cattle, elimination occurs primarily through biliary excretion.

Flunixin persists in inflammatory tissues[6] and is associated with anti-inflammatory properties which extend well beyond the period associated with detectable plasma drug concentrations.[4,6] 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
$AUC_{2\text{-last}}$ (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
$AUC_{2\text{-last}}$: 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:

1. Johansson M, Anler EL. Gas chromatographic analysis of flunixin in equine urine after extractive methylation. *J Chromatogr.* 1988; 427:55-66.
2. 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.
3. 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.
4. 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.
5. Hardee GE, Smith JA, Harris SJ. Pharmacokinetics of flunixin meglumine in the cow. *Res Vet Sci.* 1985; 39:110-112.
6. 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 dermal 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 (cm^2) 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 cm^2) compared to the dyed saline-treated control group (-4.14 kgf and -2.70 cm^2). In the Kansas study, the treatment success rate was significantly different ($p = 0.0387$) 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 cm^2) compared to the dyed saline-treated control group (-0.54 kgf and -0.96 cm^2).

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.BanamineTD.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.
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