

Banamine® Transdermal (flunixin transdermal solution) Technical Bulletin

Efficacy of flunixin meglumine transdermal administration in a tissue cage model of inflammation.¹

Background

Banamine® Transdermal (flunixin transdermal solution) is the first and only FDA-approved product for pain control in a food producing animal. It is approved for the control of pyrexia (fever) due to acute mastitis and bovine respiratory disease and for the control of pain due to foot rot. It also is the first and only non-steroidal anti-inflammatory (NSAID) cattle product available as a pour-on.

Flunixin is widely used for its anti-inflammatory and analgesic properties in veterinary practice. Its mechanism of action is believed to be primarily via the inhibition of cyclooxygenase (COX) enzymes. The determination of PGE₂ concentration in in-vivo exudate was used as an indicator of cyclooxygenase COX-2 activity.

Subcutaneously implanted tissue cages are extensively used in many animal species to study the mechanism and time course of the acute non-immune inflammatory response.^{1,2,3,4} Tissue cage studies have shown that flunixin is present in higher concentration in inflammatory exudate than in corresponding plasma.⁴

- The non-steroidal anti-inflammatory drugs inhibit the enzymes of the *arachidonic acid cascade* in an inflammatory response (Figure 1).
- Flunixin meglumine is a non-specific inhibitor of COX-1 and COX-2 enzymes.

Objective

This study was conducted to determine the effect of flunixin meglumine administered topically on the production of prostaglandin E₂ in tissue exudate.

Materials and Methods

Twelve healthy calves – 11 Holstein and one Montbeliard – were enrolled in the study. The six males were an average age of 17 months, and the six females were an average age of 3 years.¹

Four sterile spherical perforated polypropylene tissue cages were surgically embedded in the subcutaneous space at four sites per animal – two on each side of the animal's flank. A two-week post-implant stabilization period was then allowed to elapse before beginning the first study period.

Inflammation was induced by intra-caveal injection of 0.5 mL 2% sterile carrageenan solution (Figure 2). Carrageenan solution is a seaweed extract used in studies to induce inflammation.¹

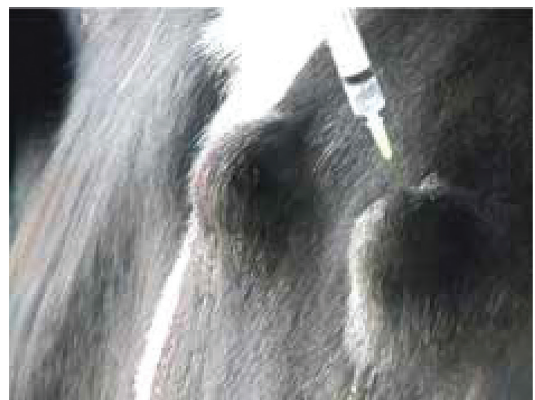
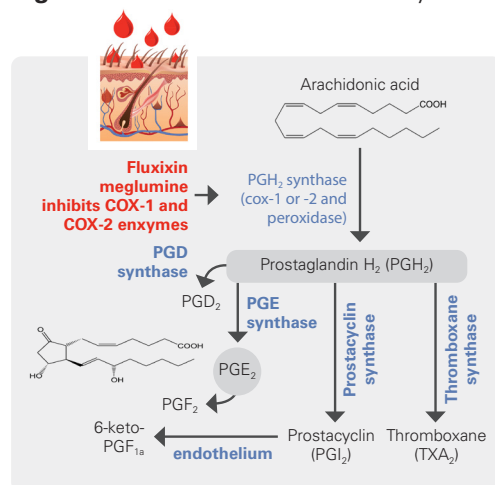
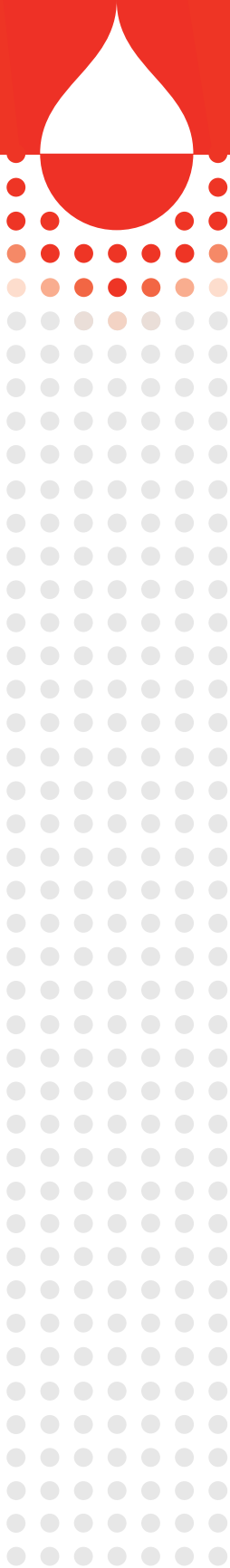


Figure 2. Injection of carrageenan solution into a tissue cage.

Figure 1. Arachidonic Acid Pathway



**Banamine®
Transdermal**



A two-period, two-sequence, two-treatment, Latin square crossover design was followed, such that each animal received flunixin or the negative control (saline) sequentially.

Animals were randomly allocated to one of the two treatment sequences. A wash-out period of three weeks was implemented between periods. During each of the study periods, six animals were administered flunixin meglumine (3.3 mg/kg BW) by transdermal route (pour-on); the other six received saline by the same application route. All administrations were made at time zero of each period, immediately after induction of inflammation.¹

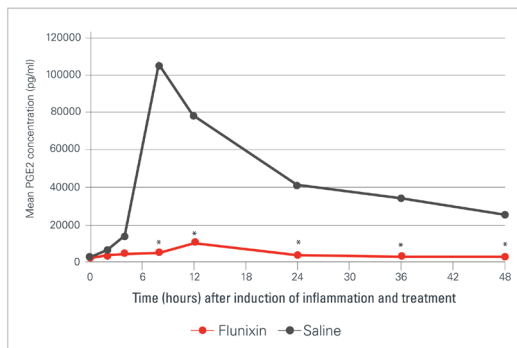
Exudate was collected prior to challenge and 2, 4, 8, 12, 24, 36 and 48 hours after. Cages were emptied after each collection. Exudates collected from three out of four cages per animal were pooled at each time point.

Determination of individual PGE₂ concentration was made per time point per period. A validated method using liquid chromatography coupled with mass spectrometry was used to quantify PGE₂ concentration.¹

Results

In saline-treated animals, PGE₂ concentration levels displayed a sharp increase, the peak eight hours post-challenge, and a gradual decrease over time (PGE₂ concentration levels were still elevated 48 hours after challenge) (Figure 3).

Figure 3. Mean PGE₂ concentrations (pg/mL) according to treatment (two periods) (*: *P* < 0.05).



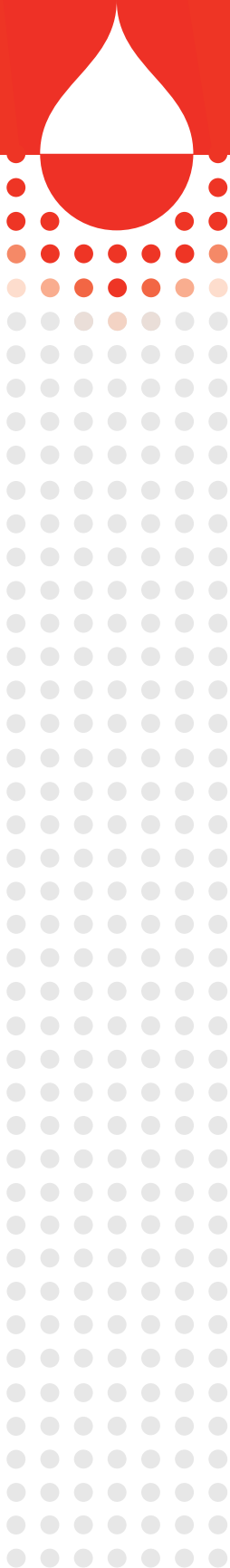
In flunixin meglumine treated animals, PGE₂ peak occurred later (12 hours after challenge) and was strongly reduced (less than 10 percent of level in present control animals). PGE₂ concentrations were significantly lower than those measured after saline administration over entire time period.

The percentage reduction of PGE₂ concentration in treated animals relative to controls was close to or more than 90 percent at peak PGE₂ concentrations (eight and 12 hours after challenge), and inhibition lasted until the end of the animal phase (Table 1).

Table 1. PGE₂ concentrations: flunixin compared to saline.

| Time after treatment | % reduction of PGE ₂ compared to Saline | Ratio of PGE ₂ Saline / flunixin |
|----------------------|--|---|
| +2h | 44% | 1.8 |
| +4h | 64% | 2.8 |
| +8h | 95% | 19.1 |
| +12h | 87% | 7.8 |
| +24h | 90% | 9.9 |
| +36h | 90% | 9.7 |
| +48h | 87% | 7.9 |

The log ratio of concentrations was significantly different between flunixin and saline (*P* < 0.05) at hours 8, 12, 24, 36 and 48, but not significantly different at hours two and four (*P* > 0.05).



Conclusions

This study showed that, compared to saline, flunixin meglumine topical significantly reduced PGE₂ concentrations from eight to 48 hours after treatment.

- **Rapid speed of action.** PGE₂ suppression occurred eight hours post-administration and lasted throughout the 48-hour measurement period.
- **Potent inhibitor of COX enzymes.** Nearly 20 times less PGE₂ compared to saline at eight hours post-treatment.
- **Extended activity.** Almost 90 percent of inhibition of PGE₂ up to 48 hours post-treatment.

¹THIRY J. *et al.*: Evaluation of flunixin meglumine pour-on administration on prostaglandin E₂ concentration in inflammatory exudate after induction of inflammation in cattle. *Res. Vet. Sci.*, 2017, 114, 294-296.

²SIDHU P. *et al.*: Tissue chamber model of acute inflammation in farm animal species. *Res. Vet. Sci.*, 2003, 74, 67-77.

³LANDONI M. *et al.*, Comparison of the anti-inflammatory actions of flunixin and ketoprofen in horses applying PK/PD modelling. *Equine Vet Journal*, 1995. Vol. 27, Issue 4, pages 247-256.

⁴CHENG Z. *et al.*, Pharmacokinetic studies of flunixin meglumine and phenylbutazone in plasma, exudate and transudate in sheep. *Journal of Vet Pharm. and Ther.*, 1998, Vol. 21, Issue 4, pages 315-321.

IMPORTANT SAFETY INFORMATION: NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN. Milk that has been taken during treatment and for 48 hours after treatment must not be used for human consumption. Cattle must not be slaughtered for human consumption within 8 days of the last treatment. Not for use in replacement dairy heifers 20 months of age or older or dry dairy cows; use in these cattle may cause drug residues in milk and/or calves born to these cows or heifers. Not for use in beef and dairy bulls intended for breeding over 1 year of age, beef calves less than 2 months of age, dairy calves, and veal calves. Do not use within 48 hours of expected parturition. Approved only as a single topical dose in cattle. For complete information on Banamine® Transdermal, see accompanying product package insert.

Banamine®
Transdermal

BanamineTD.com

Product Information

Approved by FDA under NADA # 141-450

Banamine® Transdermal (flunixin transdermal solution) Pour-On for Beef and Dairy Cattle 50 mg/mL

Non-Steroidal Anti-inflammatory Drug

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 monopalmitate NF qs.

INDICATIONS: Banamine Transdermal pour-on is indicated for the control of pyrexia associated with bovine respiratory disease and acute bovine mastitis, and the control of pain associated with foot rot in beef cattle 2 months of age and older and dairy cattle.

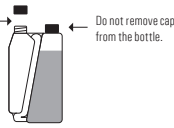
Not for use in beef and dairy bulls intended for breeding over 1 year of age, replacement dairy heifers over 20 months of age, dry dairy cows, dairy calves, or veal calves.

DOSE 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 the doses up to the nearest weight increment on the dosing chamber. If pyrexia, or the pain associated with foot rot persists, the diagnosis should be re-evaluated and alternative therapy considered. 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.

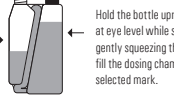
Step 1

On first use remove cap and peelable seal from the dosing chamber.



Step 2

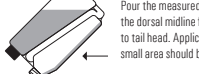
Hold the bottle upright and at eye level while slowly and gently squeezing the bottle to fill the dosing chamber to the selected mark.



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

Step 3

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

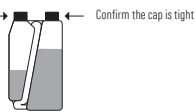


A small amount of liquid will remain on the walls of the chamber, but the chamber is calibrated to account for this.

OVERFILL REDUCTION INSTRUCTIONS

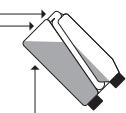
Step 1

Re-apply cap to dosing chamber and tighten.



Step 2

Tilt the bottle to allow an air pocket to 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.

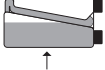


Figure 1 - Recommended pour-on location



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.

Withdrawal Periods and Residue Warnings:

Milk that has been taken during treatment and for 48 hours after treatment must not be used for human consumption. Cattle must not be slaughtered for human consumption within 8 days of treatment. Not for use in replacement dairy heifers 20 months of age or older or dry dairy cows; use in these cattle may cause drug residues in calves born to these cows or heifers. Not for use in beef calves less than 2 months of age, dairy calves, and veal calves. A withdrawal period has not been established for this product in pre-ruminating calves. Approved only as a single topical dose in cattle. Repeated treatments may result in violative residues in milk or in edible tissues.

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. Banamine Transdermal is approved only as a single topical dose. The safety of repeated treatment has not been evaluated.

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 toxicologic effect. The use of NSAIDs in the immediate post-partum period may interfere with uterine involution and the 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 beef and dairy bulls intended for breeding over 1 year of age because reproductive safety has not been evaluated.

CLINICAL PHARMACOLOGY: Flunixin meglumine is a nonsteroidal, anti-inflammatory drug. It is a weak acid (pKa = 5.62) 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.^{4,5} 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 _{0-2h} (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_{0-2h}: 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.* 1989; 427:55-60.
- 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 F2α 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 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:

Clinical field studies - bovine respiratory disease

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 control 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 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 control group (4/25, 16%).

Induced infection model studies - foot rot

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 control 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 control group (1/15, 6.7%); 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 control group (-4.14 kgf and -2.70 cm²). 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 control 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 control group (-0.54 kgf and -0.96 cm²).

Clinical field study - acute bovine mastitis

The effectiveness of flunixin transdermal solution for the control of pyrexia associated with acute bovine mastitis was demonstrated under a range of environmental temperatures (37.4 °F to 86 °F) in a multi-site field study conducted in France, Germany, and Spain. Cattle were housed in a manner which did not prevent them from licking themselves or other cows. Lactating dairy cows were enrolled when they exhibited acute signs of mastitis in one or two quarters (based on an evaluation of udder firmness, swelling, and pain), milk characteristics consistent with mastitis, and a rectal temperature of at least 104 °F.

Enrolled cows were administered either flunixin transdermal solution (3.3 mg flunixin/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 control group. A treatment success was defined as a drop in rectal temperature of ≥ 2 °F in an individual animal. The treatment success rate was significantly different (p < 0.0001) and higher in the flunixin transdermal solution-treated group (61/64, 95%) compared to the dyed saline control group (23/66, 35%).

CONTACT INFORMATION:

For technical assistance or to report a suspected adverse drug experience, call: 1-800-211-3573. For customer service or to request a Safety Data Sheet (SDS), call: 1-800-521-5767. 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 www.fda.gov/epdr/animalmae.

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>.

Approved by FDA under NADA # 141-450.

Use Only as Directed.

Copyright © 2017-2022 Merck & Co., Inc., Rahway, NJ, USA and its affiliates. All rights reserved. Formulated in Germany.

Distributed by: Intervet Inc. d/b/a Merck Animal Health, Madison, NJ 07940

Rev. 10/2022



Copyright © 2022 Merck & Co., Inc., Rahway, NJ, USA and its affiliates. All rights reserved.

merck-animal-health-usa.com • 800-521-5767

MAHCattle.com • 800-521-5767

© 2023 Merck & Co., Inc., Rahway, NJ, USA and its affiliates. All rights reserved. US-FIN-230100008 2/23