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 pain associated with foot rot and fever associated with bovine respiratory disease in cattle. 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. Tissue cage studies have shown that flunixin is present in higher concentration in inflammatory exudate than in corresponding plasma.

- The NSAIDs 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
The study was conducted to determine the effect of flunixin meglumine administered topically on the production of prostaglandin E 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.

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.

Figure 1. Arachidonic Acid Pathway

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

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.

**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).

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 of 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>
<thead>
<tr>
<th>Time after treatment</th>
<th>% reduction of PGE2 compared to Saline</th>
<th>Ratio of PGE2 Saline/flunixin</th>
</tr>
</thead>
<tbody>
<tr>
<td>+2h</td>
<td>44%</td>
<td>1.8</td>
</tr>
<tr>
<td>+4h</td>
<td>54%</td>
<td>2.8</td>
</tr>
<tr>
<td>+8h</td>
<td>95%</td>
<td>19.1</td>
</tr>
<tr>
<td>+12h</td>
<td>97%</td>
<td>7.8</td>
</tr>
<tr>
<td>+24h</td>
<td>90%</td>
<td>9.9</td>
</tr>
<tr>
<td>+36h</td>
<td>90%</td>
<td>9.7</td>
</tr>
<tr>
<td>+48h</td>
<td>87%</td>
<td>7.9</td>
</tr>
</tbody>
</table>

Table 1. PGE2 concentrations: flunixin compared to saline.

The log ratio of concentrations is significantly different between flunixin and saline (linear mixed model, p values <0.05) at hours 8, 12, 24, 36 and 48, but are not significantly different at hours two and four (p values >0.05).

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

This study shows that flunixin meglumine applied topically inhibits carrageenan-induced subcutaneous inflammation in cattle. Compared to saline, flunixin meglumine topical significantly reduced PGE2 concentrations from eight to 48 hours after treatment.

- **Rapid speed of action.** The percentage of reduction of PGE2 was demonstrated at two hours after treatment.

- **Potent anti-inflammatory activity.** 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.


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.

BanamineTD.com
Banamine Transdermal (Flunixin transdermal solution)

Product Description

NADA #141-456. Approved by FDA.

Banamine® Transdermal (Flunixin transdermal solution)

For Use On Beef and Dairy Cattle 50mg/mL.

- Non-Sterosi-Anti-Inflammatory Drug

Only for use in healthy and dairy cattle. Not for use in inbred cattle interbred for breeding, dairy bulls, dairy female 20 months of age or older, including dry cows, and lactating heifers, dairy cows, beef bulls intended for slaughter, and replacement dairy heifers under 20 months of age.

DESCRIPTION: Each milliliter of Banamine Transdermal pour-on contains 50 mg flunixin meglumine (equiv to Flunixin meglumine, 75 mg; flunixin, 50 mg; 50 mg propylene glycol dicaprylate/dicaprate NF, 0.20 mg FD&C Red No. 40, and glycerol monostearate NF). INDICATIONS: Banamine Transeraman on is indicated for the control of pyrexia associated with bovine respiratory disease and of controlled pain associated with not in chronic, hoof disorders, bone, joint and soft tissue inflammations, and surgery.

DOSE AND ADMINISTRATION: Apply once only at a dose of 3.3 mg/kg body weight. Do not give to cattle weighing less than 250 lb (<115 kg). For beef bulls, body weight should be about 900 lb (410 kg) or greater. For dairy cattle, body weight should be about 1,100 lb (500 kg) or greater.

At the time of application, the pour-on should be dispensed into a dosing chamber. The dosing chamber must then be held firmly and directed toward the back of the rump of the animal. The pour-on is dispensed from the dosing chamber and is automatically expelled into the rump region of the animal through the transfer tube.

Step 1: Squeeze the dosing chamber cap and peelable from the bottle.

Step 2: Hold the bottle upright and at eye level and gently pull the bottle cap and peelable from the bottle until the dosing chamber is to the selected mark.

Step 3: Pour the measured volume on the dorsal midline from the selected mark.

Application to a small animal should be avoided.

A small amount of liquid will remain on the walls of the chamber, but this chamber is designed to accommodate this.

OVERALL REDUCTION IN TOTAL LAMENESS:

Flunixin persists in inflammatory tissues and is associated with anti-inflammatory properties which extend well beyond the period associated with detectable plasma drug concentrations. Therefore, prediction of drug concentrations based on 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.

Flunixin produces a transient reduction in pain following single administration and interdigital swelling criteria. Flunixin transient solution-treated group (10/12, 83.33%) were statistically significantly different (p= 0.0024 and p<0.0001, respectively) and higher for the Banamine transdermal solution-treated group compared to the treatment success rate in the flunixin transient solution-treated group (1/12, 8.33%).

TARGET ANIMAL SAFETY:

In a target animal safety study in 12 six-month-old beef cattle (90 castrated males and 16 females), flunixin transdermal solution was administered topically at a dose of 3.3 mg/kg body weight to 10 animals Banamine Transdermal Days 1, 2, and 3 (at the labeled administration frequency). Cattle were continuously restrained to prevent feeding. In the study, the cattle were exposed to warm environmental conditions (72°F to 91°F) and were fed a diet of Adams® 31 and 32 in the morning of Day 1 and for the remainder of the study. On Day 1, 2, and 3, the cattle were scored on a 5-point scale for lameness (0 = normal, scoring up to 4 = severe lame) to assess the clinical effect of the treatment. No treatment-related adverse events were observed.

USER SAFETY WARNINGS:

Flunixin is for use in human. Keep out of reach of children. Flunixin transdermal solution is a potent non-steroidal anti-inflammatory drug (NSAID), and reaction may cause gastrointestinal irritation and bleeding, ileus, and central nervous system effects.

This product has been shown to cause severe and potentially irreversible eye damage (confrontation test) in rabbit eyes of both sexes, and in guinea pigs, rats, and mice. The product should be used with extreme caution. Use should be self-protection eye protection (face shield, safety glasses, or goggles); to protect eye contact; and to observe the conjunctivitis in guinea pigs, an aleve-prone skin site and pantol to prevent skin contact/or drug absorption. Wash hands after use.

In case of accidental eye contact, flush eyes immediately with water and seek medical attention.

In case of accidental skin contact and/or clothing contamination use skin thoroughly with soap and water. In case of ingestion do not induce vomiting and seek medical attention immediately.

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

In the event of ingestion do not induce vomiting and seek medical attention immediately.

Do not use Banamine Transdermal pour-on for any indication other than stated on the label. Do not use Banamine Transdermal pour-on within 48-hours of expected parturition. Do not use in animals showing signs of pregnancy.

CONTRAINDICATIONS: This product is contraindicated in the following conditions: known hypersensitivity to flunixin meglumine, or any component of the Banamine Transdermal pour-on product.

In the event of overfilling of the dosing chamber, the overfill reduction instructions contained in the product insert should be followed.

RESIDUE WARNINGS:

Cattle must not be slaughtered for human consumption within 8 days of the last treatment. Not for use in dairy cattle 20 months of age or older. Due to the potential for flunixin to be absorbed across the rumen wall during ruminating, the potential for flunixin to be absorbed into the systemic circulation of treated cattle must be considered when feeding treated cattle to beef cattle after slaughter. The residue potential in treated cattle may cause drug residues in milk and/or in calves born to these cows or heifers.

PRECAUTIONS:

Flunixin meglumine is a non-steroidal, anti-inflammatory drug (NSAID). Flunixin meglumine has been associated with interference with uterine involution and expulsion of fetal membranes. NSAIDs, corticosteroids, or potentially nephrotoxic drugs should be avoided or used only with careful monitoring because of the potential increase of adverse events.

When using products containing flunixin meglumine (Equine, bovine, and canine) it may be necessary to carefully monitor the patient for signs of azotemia or other renal disorder, due to the potential for flunixin meglumine to cause drug residues in milk and/or in calves born to these cows or heifers.

The use of NSAIDs, corticosteroids, or potentially nephrotoxic drugs should be avoided or used only with careful monitoring because of the potential increase of adverse events.

If wearing contact lenses, flush eyes immediately with water before proceeding.

If skin irritation or rash occurs, stop use and wash skin thoroughly with soap and water.

Flunixin meglumine is a non-steroidal, anti-inflammatory drug (NSAID) and a 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. NSAIDs 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 uterine tract. There may be a delay in the onset of estrus in animals treated in the phase of estrus following the NSAID treatment. NSAIDs are known to block uterine contractility through a tocolytic effect. The use of NSAIDs in the immediate postpartum period may be associated with a delay in the onset of estrus.

Cows should be monitored carefully for decreased estrus and return to estrus of lactating cattle and non-pregnant females.

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