Date of Approval: July 21, 2017

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-450

Banamine® Transdermal

flunixin transdermal solution

Steers, beef heifers, beef cows, beef bulls intended for slaughter, and replacement dairy heifers under 20 months of age

For the control of pyrexia associated with bovine respiratory disease and the control of pain associated with foot rot

Sponsored by:

Intervet, Inc.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 141-450

B. Sponsor

Intervet, Inc.
2 Giralda Farms
Madison, NJ 07940

Drug Labeler Code: 000061

C. Proprietary Name

Banamine® Transdermal

D. Product Established Name

Flunixin transdermal solution

E. Pharmacological Category

Non-steroidal anti-inflammatory

F. Dosage Form

Solution

G. Amount of Active Ingredient

50 mg/mL

H. How Supplied

100 mL, 250 mL, and 1L multiple-dose bottles

I. Dispensing Status

Rx

J. Dosage Regimen

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.

K. Route of Administration

Transdermal

L. Species/Class

Cattle/steers, beef heifers, beef cows, beef bulls intended for slaughter, and

replacement dairy heifers under 20 months of age.

M. Indications

For the control of pyrexia associated with bovine respiratory disease and the control of pain associated with foot rot

II. EFFECTIVENESS

A. Dosage Characterization:

A series of exploratory studies were conducted to evaluate the effects of breed, age, repeated doses, and environmental temperatures on plasma flunixin concentrations in healthy cattle and the control of pyrexia in cattle with bovine respiratory disease (BRD). From these studies it was concluded that the range of doses to further evaluate the effect of a single topical administration of flunixin for the control of pyrexia associated with BRD was 2.5 to 5.0 mg flunixin/kg body weight (BW), and the rectal temperatures should be measured at six hours post-treatment.

A dose response study was conducted in cattle with naturally-occurring BRD under field conditions in the United States. The enrollment criteria included abnormal respiration, abnormal attitude, and a rectal temperature of 104.5 °F or higher. A total of 150 cattle meeting enrollment criteria were randomized to one of six treatment groups: saline with 0.02% w/v red dye added for masking purposes at a dose of 1 mL/10 kg BW (negative control); Banamine® (flunixin meglumine injection) at a dose of 2.2 mg flunixin/kg BW (positive control) plus saline with 0.02% w/v red dye at a dose of 1 mL/10 kg BW (negative control); flunixin transdermal solution at a dose of 2.5 mg flunixin/kg BW; flunixin transdermal solution at a dose of 3.3 mg flunixin/kg BW; flunixin transdermal solution at a dose of 5.0 mg flunixin/kg BW; and flunixin transdermal solution at a dose of 6.6 mg flunixin/kg BW. Banamine® was administered intravenously; the dyed-saline control and flunixin transdermal solution were administered topically. The study was conducted in the winter when daily average temperatures ranged from 2 ºF to 20 ºF on days when animals were enrolled in the study and treated.

The rectal temperature of each animal was measured six hours after treatment. The drop in rectal temperature from the time of enrollment to six hours after treatment was calculated for each animal. The primary effectiveness criterion was the treatment success rate at six hours post-treatment. An animal was designated as a treatment success when the rectal temperature decreased by ≥ 2 °F from the inclusion rectal temperature at six hours (+/- 15 minutes) post-treatment. An analysis of the results indicated that all treatments were statistically different from and had higher treatment success rates than the dyed-saline negative control group. Within the flunixin transdermal solution-treated groups, the groups treated with the three highest doses (3.3 mg flunixin/kg BW, 5.0 mg flunixin/kg BW, and 6.6 mg flunixin/kg BW) were significantly different from and had higher treatment success rates than the group treated with 2.5 mg flunixin/kg BW but were not statistically different from each other.

Based on the results of this study, a single topical dose of 3.3 mg/kg was selected for evaluation in clinical field studies conducted to provide substantial evidence of effectiveness for the control of pyrexia associated with BRD. The single topical

dose of 3.3 mg/kg was also used in the experimentally-induced infection model studies to provide substantial evidence of effectiveness for the control of pain associated with foot rot.

B. Pharmacokinetic Studies

Pharmacokinetic (PK) data were generated to characterize the plasma concentration profile of flunixin transdermal solution in cattle. These studies characterized the effect of licking and environmental temperature on flunixin absorption. In addition, dose proportionality was confirmed (between the doses of 2.5 and 16.5 mg flunixin/kg BW) by evaluating the flunixin plasma concentrations generated as part of the margin of safety study and through an inter-study comparison.

Comparative Bioavailability Study

Comparison of Flunixin Plasma Levels Following a Single Dose of Flunixin Transdermal Solution to Cattle Allowed or Prevented from Licking in a Cross-over Study (Study E09-057-01)

Study E09-057-01 was a two-period, two-sequence crossover study with 24 cattle assigned randomly to two treatment groups: Group I was prevented from licking in Period 1 and allowed to lick in Period 2; Group II was allowed to lick in Period 1 and prevented from licking in Period 2. Plasma samples for flunixin analysis were collected for up to 36 hours post-dose and were analyzed using a validated LC-MS/MS method. A summary of PK results is provided in Table II.1.

Table II.1: Average (+/- standard deviation [SD]) PK parameters after a single topical administration of flunixin transdermal solution at a dose of 2.5 mg flunixin/kg BW 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.

Based upon the comparative bioavailability study, it was concluded that animals

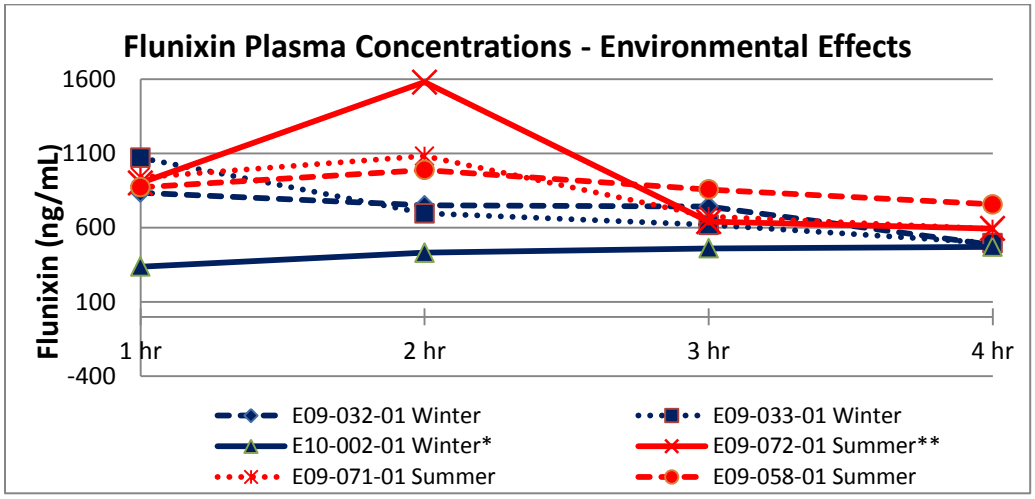
prevented from licking tended to exhibit higher plasma flunixin concentrations compared to those that were permitted to lick. Accordingly, effectiveness studies were designed to allow cattle to lick and the margin of safety study was designed to prevent cattle from licking.

Effect of Environmental Temperature on Flunixin Absorption

A series of PK studies were conducted to evaluate the effect of environmental temperature on flunixin absorption. The studies were conducted in beef cattle of various breeds. Each study included 12 to 25 animals of both genders. Flunixin transdermal solution was administered as a single topical dose of 2.5 mg flunixin/kg BW on the dorsal midline. Environmental temperatures across studies ranged from an average low of 15.3 to 20.1 °F (the coldest study) to an average high of 80 to 100 °F (the warmest study).

As illustrated in an inter-study comparison of flunixin plasma concentrations (Figure II.1.), absorption of flunixin administered topically to cattle varies as a function of environmental temperature. Furthermore, in the study associated with the lowest environmental temperatures (E10-002-01), the time to reach peak plasma concentration (Tmax) was at least 4 (+/- 2.31) hours (the last sampling point) vs. the average of 1.75 (+/- 0.5) hours in all summer studies.

Figure II.1: Inter-study comparison of flunixin plasma concentrations in cattle exposed to different environmental conditions.



*Winter study with lowest environmental temperatures
**Summer study with highest environmental temperatures.

Based upon these results, it was concluded that target animal safety should be evaluated in warm weather and that effectiveness should be confirmed across a wide range of environmental conditions.

Dose proportionality of flunixin after topical administration in cattle

Results from several PK studies, including toxicokinetic (TK) data from the margin of safety study (see Section III.A. below), were used to assess dose proportionality. There was an approximate linearity in dose response observed between the doses of 2.5 and 16.5 mg flunixin/kg BW. Therefore, it was

concluded that the results of the licking study and exploratory PK studies determining the effect of environmental temperature on flunixin exposure, which were conducted at the dose of 2.5 mg flunixin/kg, could be extrapolated to the label dose of 3.3 mg flunixin/kg.

C. Substantial Evidence:

1. Control of pyrexia associated with bovine respiratory disease

   Substantial evidence of effectiveness was demonstrated in a multi-site clinical field study and a single site clinical field study (to independently confirm effectiveness in cold environmental conditions).

   a. Multi-site Clinical Field Study

      Title: "Clinical effectiveness of flunixin transdermal (FPO) solution for the control of pyrexia in naturally-occurring bovine respiratory disease: a multi-center pivotal field trial." (Study number S10146-00)

      Study Dates: April 2011, to May 2011

      Study Locations:

      De Soto, KS
      Canyon, TX
      Oakland, NE
      Tulare, CA

      Study Design:

      Objective: To demonstrate the effectiveness of flunixin transdermal solution for the control of pyrexia associated with BRD in cattle. The study was conducted in accordance with Good Clinical Practices (GCP).

      Study Animals: Cross-bred and pure-bred beef steers, bulls, and heifers, approximately six to ten months of age, weighing 224 to 620 lbs. Animals enrolled in the study were housed in pens by sex, with a maximum of four animals per pen, and were not restricted from licking.

      Experimental Design: At each site, cattle were enrolled in the study when they met the criteria of a respiratory score of 2 or 3, an attitude score of 2 or 3, and a rectal temperature ≥ 104.5 °F. Animals that were moribund (attitude score of 4), or had other concurrent systemic disease, a severe injury, an abnormal dorsal midline region, or a wet dorsal midline region were not enrolled.

      The following clinical scoring scales were used:

      Respiratory Scoring Scale:

      0 = Normal: no abnormal respiratory symptoms are present; respiratory 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, including one or more of the following: open-mouth breathing, abdominal breathing, and/or extended head.

Attitude Scoring Scale:

0 = Normal: bright, alert, and responsive.

1 = Mildly depressed: may stand isolated with head down, ears drooping, but responsive to stimulation.

2 = Moderately depressed: may stand 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 any antimicrobial therapy.

Drug Administration: The test article was flunixin transdermal solution (5% w/v flunixin). The control article was saline with 0.02% w/v red dye added for masking purposes. The flunixin transdermal solution and the saline with red dye were administered topically in a narrow strip along the dorsal midline from the withers to the tailhead. The hair was not parted to facilitate dosing nor was the material rubbed into the hair or skin after application. All study animals included in the statistical analysis had a dry dorsal midline at the time of dosing and were not exposed to hide-wetting moisture in the six hours following treatment.

Environmental conditions: On enrollment days, the daily average environmental temperatures recorded across the sites ranged from 42 °F to 74 °F (daily lows ranged from 30 °F to 53 °F and daily highs ranged from 47 °F to 94 °F). Significant precipitation (more than trace) was noted on one enrollment day at Site 1 and two enrollment days at Site 2. Any animals that were exposed to hide-wetting moisture were excluded from the statistical analysis.

Treatment Groups: The treatment groups are described below in Table II.2.

Table II.2: Treatment Groups

Treatment	Dosage	Number of Animals*
Saline with dye	1 mL/15 kg BW once topically	115
Flunixin	3.3. mg/kg BW (1 mL/15 kg) once topically	120

*Number of animals included in the statistical analysis

Post-Treatment Measurements and Observations: Animals were brought back to the chute within 6 hours (+/- 45 minutes) in the same order in which they were enrolled. Rectal temperatures were measured and an assessment of the application site for local adverse reactions was performed. An animal was designated as a treatment success when the rectal temperature decreased by ≥ 2 °F from the inclusion rectal temperature at six hours (+/- 45 minutes) post-treatment. The effectiveness of flunixin transdermal solution for the control of pyrexia associated with BRD was evaluated by comparing the proportion of treatment successes (treatment success rate) in the flunixin transdermal solution-treated group to the control group. Animals were observed for systemic and local (application site) adverse reactions throughout the study.

Statistical Methods: There were sixteen 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.

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.

Results: The percentage of calves classified as a treatment success was statistically significantly different ($p < 0.0001$) and higher in the flunixin transdermal solution-treated group (70/120, 58.3%) compared to the control group (7/115, 6.1%).

Adverse Reactions: There were no treatment related adverse reactions within six hours following dosing. At one site, animals were observed twice following treatment for evidence of dosing site reactions (14 to 23 days post-treatment and 27 to 36 days post-treatment. At the first observation time point, 11 of 22 flunixin transdermal solution-treated animals had mild dandruff, compared to one of 24 animals from the control group. At the second observation time point, there were three flunixin transdermal solution-treated animals with observations of mild dandruff compared to one animal in the control group.

Conclusions: The results of this study demonstrate that flunixin transdermal solution, when administered once to cattle at a dose of 3.3 mg flunixin/kg BW, is effective in warm environmental temperatures for the control of pyrexia associated with BRD.

b. Clinical Field Study to Confirm Effectiveness in Cold Environmental Temperatures

Title: "Clinical efficacy of flunixin transdermal solution for the control of pyrexia in naturally-occurring bovine respiratory disease: a single site dose response field trial." (Study Number S10113-00)

Study Dates: January 2011

Study Location: Oakland, NE

Study Design:

Objectives: To determine the effectiveness of a variety of doses of flunixin transdermal solution and to evaluate the effectiveness of flunixin transdermal solution in cold environmental temperatures. The study was conducted in accordance with Good Clinical Practices (GCP).

Study Animals: Cross-bred and pure-bred beef steers, bulls, and heifers, approximately four to twelve months of age, and weighing 360 to 702 lbs. Animals enrolled in the study were housed in pens with a maximum of six animals per pen, and were not restricted from licking.

Experimental Design: Cattle were enrolled in the study when they met the criteria of a respiratory score of ≥ 1, an attitude score of 1 or 2, and a rectal temperature ≥ 104.5 °F. Animals that had an attitude score of 3 or 4, had concurrent systemic disease or a severe injury, or an abnormal dorsal midline region were not enrolled. The following clinical scoring scales were used:

Respiratory Scoring Scale:

0 = Normal: no abnormal respiratory symptoms are present; respiratory 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, including one or more of the following: open-mouth breathing, abdominal breathing, and/or extended head.

Attitude Scoring Scale:

0 = Normal: bright, alert, and 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 any antimicrobial therapy.

Drug Administration: The test article was flunixin transdermal solution (5% w/v flunixin). The control article was saline with 0.02% w/v red dye added for masking purposes. The flunixin transdermal solution and the saline with red dye were administered topically in a narrow strip along the dorsal midline from the withers to the tailhead. The hair was not parted to facilitate dosing nor was the material rubbed into the hair or skin after application.

Environmental conditions: On enrollment days, the daily average environmental temperatures ranged from 2 ºF to 20 ºF (daily lows ranged from -6 °F to 7 °F and daily highs ranged from 10 to 37 °F). There was no significant precipitation during the study; therefore, the study animals were not exposed to hide-wetting moisture at the time of dosing or in the six hours following treatment.

Treatment Groups: There were six treatment groups in the study. However, only two of the treatment groups were used for the assessment of substantial evidence of effectiveness under cold environmental conditions. The treatment groups of interest are described below in Table II.3.

Table II.3: Treatment Groups

Treatment	Dosage	Number of Animals
Saline with dye	1 mL/10 kg BW once topically	25
Flunixin	3.3. mg/kg BW (1 mL/15 kg) once topically	25

Post-Treatment Measurements and Observations: Animals were brought back to the chute within 6 hours (+/- 15 minutes) in the same order in which they were enrolled. Rectal temperatures were measured and an assessment of the application site for local adverse reactions was performed. An animal was designated as a treatment success when the rectal temperature decreased by ≥ 2 ºF from the inclusion rectal

temperature at six hours (+/- 15 minutes) post-treatment. The effectiveness of flunixin transdermal solution for the control of pyrexia associated with BRD under cold environmental conditions was evaluated by comparing the proportion of treatment successes (treatment success rate) in the flunixin transdermal solution-treated group to the control group. Animals were observed for systemic and application site reactions throughout the study.

Statistical Methods: Treatment success rate was analyzed by a generalized linear mixed model where a binomial distribution was assumed and a logit link was used. Treatment was included in the model as a fixed effect and the residual was specified as a random effect. The contrast between the 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.

Results: The percentage of calves classified as a treatment success was statistically significantly different (p =0.0002) and higher in the flunixin transdermal solution-treated group (19/25, 76%) compared to the control group (4/25, 16%).

Adverse Reactions: There were no treatment related adverse reactions within six hours following dosing.

Conclusions: The results of this study demonstrate that flunixin transdermal solution, when administered once to cattle at a dose of 3.3 mg flunixin/kg BW, is effective in cold environmental temperatures for the control of pyrexia associated with BRD.

2. Control of pain associated with foot rot

Effectiveness of flunixin transdermal solution for the control of pain associated with foot rot was demonstrated using an experimentally-induced infection model study replicated at two independent study sites.

Title: "Effectiveness of flunixin pour on (FPO) for the control of pain associated with experimentally induced foot rot infection of *Fusobacterium necrophorum* in cattle: a multi-center pivotal study." (Study Nos. S14319-01 and S14319-02)

Study Dates:

Site 1: September 11, 2015, to April 15, 2016

Site 2: September 11, 2015, to June 23, 2016

Study Locations:

Site 1: Oakland, NE

Site 2: Manhattan, KS

Study Design:

Objective: To demonstrate the effectiveness of flunixin transdermal solution for the control of pain associated with foot rot in cattle. The studies were conducted in accordance with Good Clinical Practices (GCP).

Study Animals: Each site enrolled 30 pure-bred Holstein steers, 8 months of age, and weighing between 339 and 493 kg (746 to 1085 lbs) at Site 1, and between 326 and 470 kg (717 to 1034 lbs) at Site 2. Animals enrolled in the studies were housed in pens, with six animals per pen (three animals per treatment group per pen), and were not restricted from licking.

Experimental Design: Calves 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. Entry into the study required that calves demonstrate signs of pain associated with foot rot by meeting the following criteria: lameness score of ≥ 3 in the right front limb, lesion score of 2 or 3 in the right front interdigital space, and a swelling score of 2 or 3 in the right front interdigital space.

The following clinical scoring scales were used:

Lameness scores

1 = Normal: Calf stands and walks with a level-back posture and clinically normal gait.

2 = Mildly Lame: Calf stands with a level-back posture but develops an arched-back posture during walking. The gait remains clinically normal.

3 = Moderately Lame: Calf has an arched-back posture that is evident during standing and walking. Calf has a short-strided gait in 1 or more limbs.

4 = Lame: Calf always has an arched-back posture and gait is one deliberate step at a time.

5 = Severely Lame: Calf additionally demonstrates an inability or extreme reluctance to bear weight on the right front foot.

Lesion scores

0 = No lesion

1 = Lesion healed or healing

2 = Small (≤ ¼ the length of the interdigital space) necrotic lesion.

3 = Medium (¼ to ¾ the length of the interdigital space) necrotic lesion

4 = Large (≥ ¾ the length of the interdigital space) necrotic lesion

Swelling scores

0 = None: no swelling observed

1 = Slight: swelling observed only in the interdigital space

2 = Moderate: swelling involving the interdigital space and swelling extending into the soft tissue below the dewclaws.

3 = Severe: swelling observed in the interdigital space and around the dewclaws; coronary band on one or both toes is red and swollen; ascending swelling and cellulitis may extend above the dewclaws.

At each site, the study was designed as a randomized block design, consisting of 15 blocks, each containing one animal from each treatment group. Each pen contained three blocks of animals. The experimental unit was the individual animal.

Treatment Groups: The treatment groups are described below in Table II.4.

Table II.4: Treatment Groups

Treatment	Dosage	Number of Animals Site 1	Number of Animals Site 2
Saline with dye	1 mL/15 kg BW once topically	15	15
Flunixin	3.3 mg/kg BW (1 mL/15 kg) once topically	15	15

Drug Administration: The test article was flunixin transdermal solution (5% w/v flunixin). The control article was saline with 0.02% w/v red dye added for masking purposes. The flunixin transdermal solution and the saline with red dye were administered topically in a narrow strip along the dorsal midline from the withers to the tailhead. The hair was not parted to facilitate dosing nor was the material rubbed into the hair or skin after application. All study animals included in the statistical analysis had a dry dorsal midline at the time of dosing and were not exposed to hide-wetting moisture in the six hours following treatment.

Environmental conditions: On the day of enrollment/treatment, the daily environmental temperatures ranged from 61 °F to 85 °F at Site 1 and 27 °F to 53 °F at Site 2. No animals were exposed to hide-wetting moisture before or after dosing at either study site.

Measurements and Observations: Lameness was scored (using the scoring system described above) immediately before the induction of footrot, once daily after the induction of footrot until enrollment (approximately 48 hours after induction at both sites), at the time of enrollment (Day 0), and at six hours (+/- 30 minutes) after treatment. Lameness was observed by a single masked and experienced observer at each site, as animals walked approximately 10 to 25 feet on a hard, non-slip, level surface. An individual animal was defined as a treatment success when the lameness score

decreased by ≥1 score from the enrollment lameness score at six hours (+/- 30 minutes) after treatment.

A real-time, gait analysis system (MatScan, Tekscan, Inc.) was used to evaluate the maximum total force and contact area (at the time of maximum total force) for the right front foot before the induction of footrot, at enrollment, and at six hours (+/- 30 minutes) after treatment.

The primary effectiveness variables were the proportion of treatment successes (as defined by lameness scores), the average change in maximum total force between enrollment and six hours (+/- 30 minutes) after treatment, and the average change in contact area between enrollment and six hours (+/- 30 minutes) after treatment. At both sites animals were enrolled approximately one to two hours before treatments were administered.

In order to demonstrate the effectiveness of flunixin transdermal solution for the control of pain associated with footrot, each study site was required to independently meet both of the following criteria:

- Statistically significant difference in treatment success (lameness scores) between the treated and control groups ($p<0.05$) at six hours (+/- 30 minutes) after treatment.

AND

- Improvement in the average change in maximum total force and the contact area for the right front foot between enrollment and six hours (+/- 30 minutes) after treatment

Statistical Methods: 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 each site separately using a generalized linear mixed model with binomial distribution and logit link. The model included the fixed effect of treatment and the random effect of pen.

At each site, the average changes in the maximum total force and contact area between enrollment and 6 hours after treatment for each treatment group were compared using descriptive statistics (box plots and confidence intervals). Average changes in biometric gait parameters were also compared between the treatment groups using a linear mixed model. The model included the fixed effect of treatment and the random effect of pen. Baseline value was used as a covariate.

Results:

Table II.5: Site 1 Results

Primary variable	Control group	Flunixin transdermal solution-treated group	P-value
Lameness score improvement success (number of animals classified as a treatment success/number in treatment group)	6.67% (1/15)	100% (15/15)	0.0263*
Mean change in maximum force (kg-force) between enrollment and 6 hours post-treatment (95% confidence interval)	-4.14 kg-force (-19.82:11.54)	43.08 kg-force (30.65:55.52)	<0.0001
Mean change in contact area (cm^2) between enrollment and 6 hours post-treatment (95% confidence interval)	-2.70 cm^2 (-8.19:2.80)	16.76 cm^2 (11.48:22.04)	<0.0001

* The p-value is from a sensitivity analysis in which one success in the flunixin transdermal solution-treated group was artificially changed to a failure. The original model did not converge because there were no failures in the flunixin transdermal solution-treated group.

The mean change in maximum force across all 30 study animals between baseline (before challenge) and enrollment was -31.29 kg-force. The mean change in contact area across all 30 study animals between baseline (before challenge) and enrollment was -10.89 cm^2. Therefore, the mean increases in maximum force and contact area in the flunixin transdermal solution-treated group in the six hours after treatment were considered clinically relevant.

Table II.6: Site 2 Results

Primary variable	Control group	Flunixin transdermal solution-treated group	P-value
Lameness score improvement success (number of animals classified as a treatment success/number in treatment group)	53.33% (8/15)	93.33% (14/15)	0.0387
Mean change in maximum force (kg-force) between enrollment and 6 hours post-treatment (95% confidence interval)	-0.54 kg-force (-13.87:12.78)	34.32 kg-force (19.77: 48.86)	0.0002
Mean change in contact area (cm^2) between enrollment and 6 hours post-treatment (95% confidence interval)	-0.96 cm^2 (-8.96:7.03)	16.38 cm^2 (9.65: 23.10)	<0.0001

The mean change in maximum force across all 30 study animals between baseline (before challenge) and enrollment was -32.95 kg-force. The mean change in contact area across all 30 study animals between baseline (before challenge) and enrollment was -15.51 cm^2. Therefore, the mean increases in maximum force and contact area in the flunixin transdermal solution-treated group in the six hours after treatment were considered clinically relevant.

Adverse Reactions: No treatment-related adverse reactions were reported in the six hours following dosing.

Conclusions: Each study independently demonstrated that flunixin transdermal solution, when administered once to cattle at a dose of 3.3 mg flunixin/kg BW, is effective for the control of pain associated with foot rot.

III. TARGET ANIMAL SAFETY

The target animal safety of flunixin transdermal solution was demonstrated in a margin of safety study and supportive application site safety studies.

Pharmacokinetic studies described in Section II.B. characterized the effect of licking and environmental temperature on flunixin absorption. Study E09-057-01 demonstrated that animals prevented from licking tended to exhibit higher flunixin concentrations as compared to those that were permitted to lick. Exploratory pharmacokinetic studies evaluating the effect of environmental temperature on flunixin exposure demonstrated that the time to reach peak plasma concentration (T_{max}) was shorter in warm environmental temperatures. Therefore, the margin of safety study was designed to prevent cattle from licking and was conducted in warm weather conditions to maximize exposure.

A. Margin of Safety Study

Title: "(SCH 14714) Flunixin Transdermal Solution: 3-Day Topical Target Animal Safety Study in Growing Cattle." Study number S10052-00 (Study initiation date July 1, 2011; Study completion date September 7, 2012)

Study Location: Tulare, CA

Study Design:

Objective: To evaluate the safety of flunixin transdermal solution when administered to cattle topically at 0 (saline control), 1, 3, and 5 times the proposed clinical dose of 1 mL/15 kg BW (equivalent to 3.3 mg of flunixin/kg BW) per day for a total of three doses given on three consecutive days (which is 3 times the proposed clinical duration of a single dose administration). The study was conducted in compliance with the Good Laboratory Practice (GLP) regulations (21 CFR Part 58).

Study Animals: The study included 32 crossbred beef cattle (16 castrated males and 16 females), six months old and weighing 144 to 199 kg on Day -9. Animals were identified with duplicate ear tags.

Animals were individually housed in covered pens and were continuously restrained in stanchions to prevent licking, from acclimation through dosing until

scheduled necropsy, except for brief periods when they were moved to a squeeze chute for sample collection, examination, and weighing. Each animal had *ad libitum* access to an appropriate diet for growing cattle and *ad libitum* access to water. All study animals were euthanized at the end of the study.

Experimental Design: Within each sex, four location blocks were formed by grouping adjacent pens and then randomly assigning the four blocks within each sex to phase (A, B, C, D for staggered drug administration) using a random number generator. Within each sex and location block (phase), the four pens were randomly assigned to treatment using a random number generator.

On Study Day -8, animals selected for the study were randomly assigned to pens, and treatment groups, using simple randomization.

Drug Administration: The test article was flunixin transdermal solution (5% w/v flunixin). The control article was saline with 0.02% w/v red dye added for masking purposes. Treatments were administered topically in a narrow strip along the dorsal midline from the withers to the tailhead. The hair was not parted to facilitate dosing nor was the material rubbed into the hair or skin after application.

Animals were divided into four phases (A through D) for drug administration with one animal/sex/group. Drug administration was staggered by one day between each phase. Therefore, all study procedures were repeated over four calendar days.

Environmental conditions: On treatment days, the maximum environmental temperatures were 70 °F to 80 °F.

Treatment Groups: Treatment groups are described below in Table III.1.

Table III. 1. Treatment Groups

Group	Dosage	Number of Animals
0X	Dye in saline: 5 mL/15 kg BW topically[1] once daily on Days 0, 1, and 2	4 castrated males (CM) and 4 females (F)
1X	Flunixin: 3.3 mg/kg BW (1 mL/15 kg) topically once daily on Days 0, 1, and 2	4 CM:4 F
3X	Flunixin: 9.9 mg/kg BW (3 mL/15 kg) topically once daily on Days 0, 1, and 2	4 CM:4 F
5X	Flunixin: 16.5 mg/kg BW (5 mL/15 kg) topically once daily on Days 0, 1, and 2	4 CM:4 F

[1]Volume equivalent to the 5X treatment group

Measurements and Observations:

Physical variables (rectal temperature, respiratory rate, heart rate, mucous membrane color, and capillary refill time) were measured daily starting on Day -14.

Physical examinations were conducted on all potential study animals on Days -14

and -9, and all enrolled study animals on Days -7, -1, 1 and 3. Clinical observations were made once daily during acclimation (Day -21 to Day -15) and twice daily (at least 6 hours apart) during the pretreatment (Day -14 to Day -1) and treatment periods (Day 0 to Day 3) continuing up to the day of scheduled necropsy (Day 3), and included an evaluation of appetite, body condition, eyes, respiration, nasal discharge, locomotion/musculature, skin and hair coat, behavioral attitude, feces, and urine.

Body weights were measured on Days -21, -14, -9, -7, -1, 1 and 3.

Feed and water consumption were measured daily during the pre-treatment and treatment periods.

Blood samples were collected on Days -14, -10, -1, 1, and 3, for hematological, coagulation, and clinical chemistry analysis. Blood samples were also collected on Days 0 (prior to dosing (0-hr), and 1, 3, 6, and 12 hours after dosing), 1 (prior to dosing and 1 and 3 hours after dosing), 2 (prior to dosing and 1 and 3 hours after dosing), and 3 (24-hr after dosing) for plasma flunixin concentration.

Urine samples were collected on Days -14, -10, -1, 1, and at necropsy on Day 3 for measurement of specific gravity, an evaluation of chemical characteristics, and a microscopic examination of the sediment.

Fecal samples were collected on Days -10, -4, -1, 1, 2, and at necropsy on Day 3. Samples were examined for blood (frank and occult), color (visual), consistency (visual), and parasites (floatation on Day -14 only).

Cattle were necropsied on Day 3, the day after the final dosing. A complete gross examination was performed and a complete set of tissues and any gross lesions were collected for histopathologic examination. Weights were taken, when possible, of adrenal glands, brain, heart, kidneys, liver, ovaries, pituitary, spleen, thyroid (with parathyroid), and organ/brain weight and organ/body weight (BW) ratios were calculated.

All observations and data collection were performed by masked, trained personnel, with the exception of the pathologist who was unmasked for the histopathologic examination.

Statistical Methods:

The following variables were analyzed statistically: feed and water consumption, select parameters from the physical examination (body weight, body temperature, respiratory rate, and heart rate), individual hematology and coagulation variables, individual clinical chemistry variables, select urinalysis variables (pH and specific gravity), plasma flunixin concentration, and post-mortem organ weights.

All continuous variables were analyzed using mixed models. Mixed model repeated measures analyses with baseline covariates were used for variables measured multiple times. Three way interactions (treatment by sex by day) were tested at the 0.05 level of significance. Treatment main effect and two way interactions involving treatment were tested at the 0.1 level of significance. Results were provided in a series of graphs with the normal reference ranges noted.

Results:

Physical examinations and clinical observations: There were no mortalities and no animals were removed from the study post-treatment. One animal in the 3X group and three animals in the 5X group had one or more of the following clinical signs of application site irritation intermittently on the second and third days of dosing: twisting, kicking, rubbing on the fence, and/or prancing. The signs started approximately five minutes after dosing and all of the animals returned to normal within 30 to 60 minutes. There were no other treatment-related abnormalities observed in the physical variables or during physical examinations and clinical observations.

Feed and water consumption and body weight: Feed and water consumption was not affected by treatment. During the dosing period, nearly all animals in all treatment groups, including the control group, showed slight to moderately decreased feed consumption. The decreased feed consumption correlated with slight decreases in body weight across all treatment groups during the dosing period. The individual feed consumption and body weight changes were not consistently correlated with animals for which abomasal erosions and ulcerations were found on histopathology.

Hematology/Clinical Chemistry: Variations from the normal reference intervals were noted for some variables in individual animals and some statistically significant differences were found. However, there were no clinically significant abnormalities, no dose or time dependent trends, and no correlation with pathology findings to indicate any treatment-related effects.

Urinalysis: 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. These findings were considered treatment-related. There were no animals with clinically abnormal numbers of red blood cells in the urine sediment following treatment.

Fecal examinations: Three animals in the 5X treatment group had positive fecal occult blood: one animal on Day 1, one animal on Day 2, and one animal on Days 2 and 3. These findings were considered treatment-related. There was no visual blood seen on fecal examination in any of the animals.

Necropsy Evaluation/Histopathology: Test-article related lesions were noted in the abomasum and in the skin at the application site. Various other gross and microscopic lesions were noted in cattle from all treatment groups and were considered incidental.

In the abomasum, depressed areas were noted grossly which generally correlated to abomasal erosions and ulcerations microscopically. The abomasal erosions and ulcerations increased in incidence and severity with increasing dose as noted in Tables III.2 and III.3.

Table III.2. Gross lesions in the abomasum by treatment group

	Number of Lesions			
Gross Lesion	**0X**	**1X**	**3X**	**5X**
Depressed area; fundus; focal	0	0	0	2
Depressed area; pylorus; focal	0	2	1	1
Depressed area; pylorus; multi-focal	2	2	5	6
Total number of lesions (number of animals affected)	2 (2)	4 (4)	6 (6)	9 (8)

Table III.3. Microscopic lesions in the abomasum by treatment group

	Number of Lesions			
Microscopic Lesion	**0X[1]**	**1X**	**3X**	**5X**
Erosion, acute, pylorus, minimal	0	0	0	1
Erosion, acute, pylorus, mild	0	2	2	1
Erosion, acute, pylorus, moderate	0	0	2	3
Erosion, acute, pylorus, marked	0	0	1	2
Ulcer, acute, pylorus, minimal	0	0	2	1
Ulcer, acute, pylorus, mild	0	1	0	0
Ulcer, acute, pylorus, moderate	0	0	1	0
Ulcer, acute, fundus, mild	0	0	0	2
Total number of lesions (number of animals affected)	0[1]	3 (3)	8 (6)	10 (8)

1- One abomasal gross lesion specimen was lost and not evaluated microscopically

The abomasal erosive/ulcerative lesions correlated with sporadic positive fecal occult blood in three 5X dose level animals. There were no animals with any other evidence of gastrointestinal bleeding or clinical signs of abomasal ulceration during the study.

Application site lesions were not seen visually during the gross necropsy evaluation. The histopathology evaluation demonstrated an increase in the incidence and/or severity with increasing dose, as compared to animals in the control group, of mixed inflammatory cell infiltrates, epidermal necrosis, and dermal necrosis in both males and females in the 1X, 3X, and 5X dose groups. Acute epidermal and dermal necrosis was only found in groups treated with flunixin transdermal solution. The severity of the epidermal and dermal necrosis was minimal to mild, with a combined thickness of approximately 1 to 1.5 mm.

Pharmacokinetics: Dose proportionality was observed across the dose range of 3.3 to 16.5 mg flunixin/kg BW. There was minimal to no indication of drug accumulation after the second dose of flunixin transdermal solution. The systemic exposure of flunixin when administered topically at a dose of 3.3 mg flunixin/kg BW was markedly lower than systemic exposures observed in other studies when flunixin meglumine injectable solution was administered intravenously at a dose of 2.2 mg flunixin/kg BW.

Conclusions: This study demonstrates an acceptable safety profile for flunixin transdermal solution when administered once to cattle at a dose of 3.3 mg flunixin/kg BW. Treatment-related findings following the administration of flunixin transdermal solution at doses up to 16.5 mg/kg BW (5X the recommended dose) for three consecutive days included trace occult blood in the urine, fecal occult blood, gross pathology and histopathology observations of abomasal erosions and ulcerations, clinical signs of application site irritation, and minimal to mild epidermal and dermal necrosis at the application site. Based on a pharmacokinetic comparison of systemic exposure, the target animal safety risks associated with the use of a single topical dose of 3.3 mg flunixin/kg BW are expected to be similar to the risks associated with an intravenous dose of 2.2 mg flunixin/kg BW of Banamine® (flunixin meglumine injection) (NADA 101-479) in cattle.

B. Application Site Safety

Application site safety was evaluated in the margin of safety study (see Section III.A above) after doses of 1, 3, and 5 times the label dose of 1 mL/15 kg BW (equivalent to 3.3 mg of flunixin/kg BW) per day for a total of three doses given on three consecutive days. Application site reactions included clinical signs of twisting, kicking, rubbing on the fence, and/or prancing, which started approximately five minutes after dosing and resolved within 30 to 60 minutes. These reactions occurred after the second and third day of dosing in one of eight animals given three times the label dose and three of eight animals given five times the label dose. There were no application site reactions that were visually evident in the margin of safety study after three doses given over three consecutive days; however, minimal to mild epidermal and dermal necrosis was observed as part of the histopathologic examination.

Application site safety was also evaluated beyond three days after treatment in supportive studies and following treatment at one site in the multi-site clinical effectiveness study (Study S10146-00). In these studies, application site reactions including dandruff/skin flakes, hair damage (thin, broken, brittle hair), and skin thickening were observed. The application site reactions were first observed visually around three to seven days post-dosing and lasted for about 14 days. These reactions were cosmetic in nature and generally resolved without treatment.

C. Reproductive Safety

An inter-study comparison of flunixin $AUC_{0\text{-}inf}$ demonstrated that the systemic exposure of flunixin is markedly lower when administered topically at a dose of 3.3 mg flunixin/kg BW than when administered IV at a dose of 2.2 mg flunixin/kg BW. Therefore, the reproductive safety of flunixin transdermal solution for female reproducing cattle is supported through reproductive safety studies conducted for the supplemental approval of Banamine® (flunixin meglumine injection) for cattle. The FOI Summary for the supplemental approval of NADA 101-479 dated May 6, 1998, contains a summary of female reproductive safety studies in cattle.

IV. HUMAN FOOD SAFETY

A. Antimicrobial Resistance

This product is not an antibacterial.

B. Impact of Residues on Human Intestinal Flora

This product is not an antibacterial.

C. Toxicology

Reassessment of the toxicological ADI was not needed for this approval. The FOI Summary for the supplemental approval of NADA 101-479, dated May 6, 1998, contains a summary of all toxicology studies and information.

D. Establishment of the Final ADI

The final ADI is the toxicological ADI of 0.72 µg/kg bw/day for total residues of flunixin derived from the two-year carcinogenicity study in rats. The codified ADI is listed under 21 CFR 556.286.

E. Safe Concentrations for Total Residues in Edible Tissues

Approximately 30% of the ADI, i.e. 0.22 µg/kg bw/day (13 µg/person/day), is reserved for milk. The remaining 70% of the ADI, i.e., 0.50 µg/kg bw/day (30 µg/person/day), is applied to each edible tissue to calculate the safe concentration. The safe concentrations for total residues of flunixin in each edible tissue of steers, beef heifers, beef cows, beef bulls intended for slaughter, and replacement dairy heifers under 20 months of age are: 100 ppb for muscle, 300 ppb for liver, 600 ppb for kidney, and 600 ppb for fat.

F. Residue Chemistry

1. Summary of Residue Chemistry Studies

   a. Total Residue and Metabolism Studies

      CVM did not require total residue and metabolism studies for this approval. The FOI Summary for the supplemental approval of NADA 101-479 dated May 6, 1998, contains summaries of total residue and metabolism studies for flunixin meglumine in beef cattle.

      The sponsor provided a written discussion for why the currently assigned marker:total ratio and approved tolerances derived from it established for intravenously administered flunixin meglumine represent a worst-case scenario to address Agency concerns for the human food safety of topical residues. The sponsor provided peer-reviewed articles contending that cattle skin is essentially inert and does not contribute to first pass metabolism and that structural analogues of flunixin are not metabolized significantly upon percutaneous absorption. In addition, the sponsor referred to Study 95708, summarized under NADA 101-479 FOI Summary dated May 6, 1998, in which cattle were dosed intravenously with 3.6 mg/kg flunixin meglumine/BW for 3 days. The marker:total ratio in

cattle muscle was 0.318 at 2 days post-dose. Mean total residues in liver at 4 days post-dose were 388 ppb and 23 ppb in muscle. These data were compared to data obtained in Study 02487, summarized under NADA 141-299 FOI Summary dated November 23, 2009, in which cattle were treated once subcutaneously with Resflor Injectable Solution (2.2 mg 14C-flunixin free acid and 40 mg florfenicol/kg BW). At 7 days post-dose, the marker:total ratio in injection site muscle was 0.407. Mean total residues in liver at 7 days post-dose were 18 ppb and less than 13 ppb in leg muscle. These concentrations are consistent with intravenous administration of flunixin, considering the higher dose, multiple administrations and shorter post-dose interval for the intravenous dosing study 95708. These data also show that the marker:total ratio following intravenous administration is the most conservative. Taken together, we conclude that it is reasonable to apply the existing tolerances to the topical use of flunixin.

b. Comparative Metabolism Study

CVM did not require comparative metabolism studies for this approval. The FOI Summary for the supplemental approval of NADA 101-479 dated May 6, 1998, contains summaries of comparative metabolism studies for flunixin meglumine in beef cattle.

c. Tissue Residue Depletion Study

"A Final Residue Depletion Study of Flunixin in Beef Cattle Following Administration of Flunixin Transdermal Solution During Winter" (Intervet Study No. S11195-00)

Study Dates: March 2012, to February 2013

Study Location: Terre Haute, IN

Study Design:

Objective: The objective of this study was to determine the concentration of the marker residue, flunixin free acid, in liver, kidney, omental/renal fat, leg muscle and muscle at the application site of cattle after a single administration of 3.9 mg flunixin/kg BW flunixin transdermal solution. This study was conducted in compliance with the GLP regulations (21 CFR Part 58).

Study Animals: Twenty-five (13 male and 12 female) Angus, commercial cross-bred, and Charolais beef cattle weighing 268 to 350 kg at initiation of the study

Experimental Design: Animals were randomly assigned to one of six treatment groups (n=2 animals of each sex/group).

Drug Administration: Animals were dosed topically on the dorsum along the backbone as a thin line from the withers to the tail head with a single dose of 3.9 mg/kg BW flunixin transdermal solution.

Measurements and Observations: A control animal (male) was slaughtered 6 days before dosing began. Test animals were slaughtered at 1, 2, 3, 4, 5 and 7 days post-dose. Samples of muscle below the application site (anterior, middle and posterior), leg muscle, fat, kidney and liver were collected.

Liver Assay Results: The mean flunixin free acid residues measured by HPLC-UV are presented in Table IV.1. Mean liver residues fall below the tolerance (125 ppb) by day 3.

Table IV.1. HPLC-UV Assay – Mean Residue Concentrations (ppb ± S.D.) of flunixin free acid in Beef Cattle Liver Samples.

Withdrawal Period (days)	Liver ± S.D.
1	642.8 ± 274.9
2	141.7 ± 70.5
3	97.5 ± 49.5
4	81.6 ± 21.5
5	58.7 ± 8.4
7	44.3 ± 20.3
LOQ (ppb)	15

Application Site Muscle Results: The mean flunixin free acid residues measured by LC-MS/MS are presented in Table IV.2.

Table IV.2. LC-MS/MS Assay – Mean Residue Concentrations (ppb ± S.D.) of flunixin free acid in Beef Cattle Application Site Muscle Samples.

Withdrawal Period (days)	Core Muscle ± S.D.	Ring Muscle ± S.D.
1	103.7 ± 120.6	75.8 ± 65.6
2	12.2 ± 8.3	23.8 ± 36.9
3	11.4 ± 5.2	3.5 ± 0.5
4	6.0 ± 5.7	4.6 ± 2.6
5	2.0 ± 0.4	1.8 ± 0.7
7	1.8 ± 0.8	1.3 ± 0.4
LOQ (ppb)	0.5	0.5

Fat, Kidney and Leg Muscle Results: The mean flunixin free acid residues measured by LC-MS/MS are presented in Table IV.3.

Table IV.3. LC-MS/MS Assay – Mean Residue Concentrations (ppb ± S.D.) of flunixin free acid in Beef Cattle Fat, Kidney and Leg Muscle Samples.

Withdrawal Period (days)	Fat ± S.D.	Kidney ± S.D.	Leg Muscle ± S.D.
1	13.8 ± 7.3	1092.3 ± 631	14.2 ± 4.6
2	2.9 ± 1.1	122.6 ± 46.9	5.1 ± 0.5
3	2.0 ± 0.9	62.8 ± 33.9	3.4 ± 0.6
4	1.6 ± 0.3	39.3 ± 10.8	2.9 ± 0.1
5	1.1 ± 0.3	34.1 ± 18.7	1.9 ± 0.3
7	1.3 ± 0.8	24.8 ± 19.6	1.5 ± 0.5
LOQ (ppb)	0.5	0.5	0.5

2. Target Tissue and Marker Residue

   The target tissue for residue monitoring is liver. The marker residue in edible tissues is flunixin free acid. The studies supporting the target tissue and marker residue assignments can be found under NADA 101-479 FOI Summary dated May 6, 1998.

3. Tolerances

   Per Section F1a above, we are accepting the marker:total ratios and tolerances previously assigned. Cattle tolerances are 125 ppb flunixin free acid in liver and 25 ppb flunixin free acid in muscle (21 CFR 556.286). See the FOI Summary for the supplemental approval of NADA 101-479 dated May 6, 1998.

4. Withdrawal Period

   Tissue residue data from Study No. S11195-00 were analyzed using a statistical tolerance limit algorithm that determines the upper tolerance limit for the 99th percentile of the population with 95% confidence. The data support assignment of an 8-day withdrawal period for flunixin transdermal solution when used according to label directions in steers, beef heifers, beef cows, beef bulls intended for slaughter, and replacement dairy heifers under 20 months of age.

G. Analytical Method for Residues

Cattle liver tissue residues of flunixin were measured using both the regulatory LC-UV method and a modification of the regulatory method based on simplifying the extraction procedure and determinative LC-MS/MS. There is no significant difference between the concentration data obtained using the regulatory LC-UV method and the LC-MS/MS method. Both methods are available on file at CVM.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Banamine® Transdermal:

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.

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data demonstrate that Banamine® Transdermal, when used according to the label, is safe and effective 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. Additionally, data demonstrate that residues in food products derived from species treated with Banamine® Transdermal will not represent a public health concern when the product is used according to the label.

A. Marketing Status

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is needed to appropriately diagnose and subsequently prescribe this product for use to control pyrexia associated with bovine respiratory disease and pain associated with foot rot in cattle and to monitor the safe use of the product including treatment of any adverse reactions.

B. Exclusivity

Banamine® Transdermal, as approved in our approval letter qualifies for THREE years of marketing exclusivity beginning as of the date of our approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(ii) of the FD&C Act because the sponsor submitted an original NADA that contains new studies that demonstrate the safety and effectiveness of Banamine® Transdermal.

C. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.