Date of Approval: December 23, 2022

# FREEDOM OF INFORMATION SUMMARY

## SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-450

Banamine® Transdermal

(flunixin transdermal solution)

Solution

Cattle: 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.

This supplement provides for 1) the addition of a therapeutic indication "for the control of pyrexia associated with acute bovine mastitis"; 2) the addition of the lactating dairy cow target animal subclass for all approved indications; and 3) a milk discard time.

Sponsored by:

Intervet, Inc.

## Executive Summary

This supplemental approval of Banamine® Transdermal (flunixin transdermal solution) provides for 1) the addition of a therapeutic indication "for the control of pyrexia associated with acute bovine mastitis"; 2) the addition of the lactating dairy cow target animal subclass for all approved indications; and 3) a milk discard time. Banamine® Transdermal is a topical non-steroidal anti-inflammatory drug.

FDA previously approved Banamine® Transdermal 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. Banamine® Transdermal is now approved 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. The drug is 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.

## Safety and Effectiveness

The sponsor conducted a multi-site, natural infection, field study to show that Banamine® Transdermal controls pyrexia associated with acute bovine mastitis. The study included lactating dairy cows of various breeds (primarily Holstein) ranging in age from 2 to 12 years from farms in France, Germany, and Spain. Cows were enrolled if they had clinical signs of acute bovine mastitis in one or two quarters, including defined levels of at least two signs of udder inflammation (swelling, pain, and/or firmness) and abnormal milk characteristics (thick flakes and/or abnormal appearance, color, or consistency) as well as a fever of at least 104 °F.

Cows in the treatment group received a single topical dose of Banamine® Transdermal and cows in the control group received a single topical dose of a saline control product colored with red dye. A cow was considered a treatment success for the control of pyrexia if its rectal temperature was at least 2 °F lower 6 hours after treatment compared to its rectal temperature at enrollment. There was a significant difference in treatment successes between groups, with more cattle in the Banamine® Transdermal group that were treatment successes than in the dyed saline control group.

FDA did not require further effectiveness data for the approval of Banamine® Transdermal in lactating dairy cows for the control of pyrexia associated with bovine respiratory disease and the control of pain associated with foot rot.

The Freedom of Information (FOI) Summary for the original approval of Banamine® Transdermal (NADA 141-450), dated July 21, 2017, contains summaries of target animal safety studies for cattle 2 months of age and older, including reproductive safety studies for female cattle.

## Human Food Safety

The FOI Summary for the supplemental approval of Banamine® Injectable Solution (NADA 101-479), dated May 6, 1998, contains a summary of all toxicology studies and information. FDA previously established an acceptable daily intake (ADI) for

flunixin as 0.72 ug/kg body weight (bw) per day and the safe concentrations as 100 parts per billion (ppb) for muscle, 300 ppb for liver, 600 ppb for kidney, 600 ppb for fat, and 10 ppb for milk. These values reflect the partition of the ADI between meat (70% of the ADI) and milk (30% of the ADI).

The FOI Summary for the original approval of Banamine® Transdermal (NADA 141-450), dated July 21, 2017, contains a summary of the tissue residue depletion study that assessed the quantity and nature of the residues in tissues derived from cattle treated with Banamine® Transdermal. For this supplemental approval, the sponsor conducted a milk residue depletion study to assess the quantity and nature of the residues in milk derived from lactating dairy cows treated with Banamine® Transdermal. FDA used this information, in combination with the ADI, safe concentration for milk, and previously established milk tolerance of 2 ppb, to establish a milk discard time of 48 hours. This supplemental approval did not change the previously established withdrawal period of 8 days.

FDA determined that there is a reasonable certainty of no harm for residues of flunixin in the edible tissues of treated cattle following human consumption when Banamine® Transdermal is used according to the labeling.

**Conclusions**

Based on the data submitted by the sponsor for Banamine® Transdermal, FDA determined that the drug is safe and effective when used according to the labeling.

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# 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. Drug 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 1 L multiple-dose bottles

## I. Dispensing Status

Prescription (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/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.

### M. Indication

For the control of pyrexia associated with bovine respiratory disease and acute bovine mastitis, and the control of pain associated with foot rot.

### N. Effect of Supplement

This supplement provides for 1) the addition of a therapeutic indication "for the control of pyrexia associated with acute bovine mastitis"; 2) the addition of the lactating dairy cow target animal subclass for all approved indications; and 3) a milk discard time.

## II. EFFECTIVENESS

### A. Dosage Characterization

This supplemental approval does not change the previously approved dosage. The FOI Summary for the original approval of NADA 141-450 dated July 21, 2017, contains dosage characterization information for cattle.

### B. Substantial Evidence

CVM did not require effectiveness studies for this supplemental approval for the use of Banamine® Transdermal for the control of pyrexia associated with bovine respiratory disease or the control of pain associated with foot rot in lactating dairy cows. The FOI Summary for the original approval of NADA 141-450 dated July 21, 2017, contains a summary of studies that demonstrate effectiveness of the drug for the control of pyrexia associated with bovine respiratory disease and the control of pain associated with foot rot in beef cattle 2 months of age and older and dairy cattle. A multi-site clinical field study in lactating dairy cows provided substantial evidence of effectiveness for the control of pyrexia associated with acute bovine mastitis.

1. Multi-Site Clinical Field Study

   **Title:** Evaluation of the Efficacy and Safety of Flunixin Transdermal Solution for the Control of Pyrexia and/or Inflammation Associated with Naturally Occurring Bovine Mastitis (Study No. S12074-00)

   **Study Dates:** March 26, 2013, to December 5, 2014

   **Study Locations:** Nineteen clinical investigators from Basseux, France; Cholet, France; Melay, France; Lege, France; Saint Pierre Montlimart, France; Amou, France; Mirepeix, France; Morhange, France; Riom es Montagne, France; St Hilaire du Harcouet, France; Yvetot, France; Cabanillas de la Sierra, Spain; Madrid, Spain; Cartagena (Murcia), Spain; Jessen (Elster), Germany; Zeven, Germany; Grossengottern, Germany; Vogelsberg, Germany; and Schimberg-Ershausen, Germany enrolled animals in the study.

   **Study Design:**

   Objective: To demonstrate the effectiveness of flunixin transdermal solution

for the control of pyrexia and/or inflammation associated with acute bovine mastitis.

Study Animals: A total of 148 cows were enrolled by 19 clinical investigators in the study. The study animals were purebred and crossbred lactating dairy cows (primarily Holstein), between 2 and 12 years of age, and weighing 430 to 844 kg (946 to 1857 lbs). Depending on the facility, cows were housed indoors or on pasture. Cows were not restricted from licking and, in most cases, were free to contact and interact with at least one other cow. They were also protected from rain and misting systems and did not have access to a cow brush between the time of treatment and the time of the post-treatment observations and measurements (6 hours +/- 1 hour).

Experimental Design: This was a multi-site, randomized, masked field study. Each individual investigator was considered a site in the experimental design and selected one or more dairy farms from their veterinary practice for the study. Each investigator (site) randomly assigned cows meeting the inclusion criteria (described below) to one of the two treatment groups in a 1:1 ratio: Banamine® Transdermal (flunixin transdermal solution) or saline colored with red dye for masking purposes.

Cows were allocated to treatments using a computer-generated random table (one table generated for each site/investigator) in the order of enrollment, regardless of which dairy farm they were on. Only treatment administration personnel and the statistician had access to treatment assignments during the study. All other personnel involved in the conduct of the study were masked to treatment assignments until after the data were locked for statistical analysis. The study was conducted in accordance with Good Clinical Practice guidelines.

Drug Administration: Cows were administered either Banamine® Transdermal (flunixin transdermal solution) containing 5% w/v flunixin free acid equivalent, once at a dose of 3.3 mg/kg bw (1 mL/15 kg bw), or saline colored with red dye once at a dose of 1 mL/15 kg bw. All assigned treatments were administered topically in a narrow strip along the dorsal midline from the withers to the tailhead on the day of enrollment (Day 0). The hair was not parted to facilitate dosing nor was the material rubbed into the hair or skin after application. No study animals included in the statistical analysis were exposed to hide-wetting moisture in the six hours following treatment.

Measurements and Observations: Cows were enrolled if they were diagnosed with acute mastitis in one or two quarters as evidenced by showing at least two of the clinical signs of udder inflammation (swelling, pain, or firmness) with scores of 2 or 3 (total inflammation score of 4 or greater), a milk characteristic score of 2 or 3, and a rectal temperature ≥ 104 °F. Animals that had mastitis in 3 or 4 quarters, were moribund, had other concurrent systemic disease, had calved within 7 days, had mastitis within 30 days, or had an abnormal dorsal midline region were not enrolled. The following tables show the clinical scoring scales that were used in the study.

**Table II.1. Udder Pain Scale Scores**

| Clinical Score | Description |
|---|---|
| 0 | Normal: No unusual reaction to palpation. |
| 1 | Mild: Cow exhibits slightly unusual reaction to palpation of the affected quarter. The reaction may include a skin tenseness or flinch. |
| 2 | Moderate: Cow exhibits a definite sensitivity in the affected quarter. The reaction may involve leg movement, considerable skin tenseness, or movement of the body away from the observer. |
| 3 | Severe: Cow exhibits aggressive reaction to approach or palpation of the affected quarter. The reaction may include kicking or rapid body movement. |

**Table II.2. Swelling Scores**

| Clinical Score | Description |
|---|---|
| 0 | Normal: No enlargement. |
| 1 | Mild: Minimally apparent enlargement of the affected quarter. Detection requires careful observation and palpation. |
| 2 | Moderate: Enlargement is readily apparent upon careful observation and palpation. |
| 3 | Severe: Dramatic enlargement that is readily apparent upon casual observation or palpation. |

**Table II.3. Firmness scores**

| Clinical Score | Description |
|---|---|
| 0 | Normal: No abnormal firmness detected. |
| 1 | Mild: Minimally apparent firmness of the affected quarter. |
| 2 | Moderate: Firmness is readily detectable upon casual palpation, but is not extreme. |
| 3 | Severe: "rock hard", difficult to push finger into parenchymal tissue. |

**Table II.4. Milk Characteristics Scores**

| Clinical Score | Description |
|---|---|
| 0 | Normal: Normal milk appearance. |
| 1 | Mild: Normal milk appearance with thin flakes. |
| 2 | Moderate: Modified milk with thick flakes. |
| 3 | Severe: Highly modified milk (colored milk, watery milk, jelly appearance, bloody milk…). |

At six hours (+/- 1 hour) after treatment, rectal temperature, udder inflammation (swelling, pain, and firmness), milk characteristics, and general attitude were observed and scored. The dosing site was visually observed and palpated for local adverse reactions. Animals were treated with intramammary and systemic antibiotics and observed for an additional 5 days; however, the effectiveness evaluation for Banamine® Transdermal was based on only the 6 hour post-treatment observations. Animals were

observed for systemic and local adverse reactions throughout the study (6 days).

From the time of enrollment until 6 +/- 1 hour after treatment, the environmental temperatures across all sites included in the statistical analysis were measured and ranged from 3 °C (37.4 °F) to 30 °C (86 °F).

The primary variables were treatment success for control of pyrexia and treatment success for control of inflammation.

Treatment success for the control of pyrexia: A cow was designated as a treatment success for the control of pyrexia when the rectal temperature decreased by ≥ 2 °F from the inclusion rectal temperature at six hours (+/- 1 hour) post-treatment.

Treatment success for the control of inflammation: A cow was designated as a treatment success for the control of inflammation if the total inflammation score (sum of swelling, pain, and firmness scores) was ≤ 2 and no individual scores had worsened by 2 or more scores at six hours (+/- 1 hour) post-treatment.

To be considered effective for the control of pyrexia associated with acute bovine mastitis, the percentage of cows classified as a success (treatment success rate) for pyrexia reduction at 6 hours post-treatment in the Banamine® Transdermal group was required to be significantly different ($P < 0.05$) and numerically higher than the treatment success rate for pyrexia reduction at 6 hours post-treatment in the dyed saline control group.

To be considered effective for the control of inflammation associated with acute bovine mastitis, the percentage of cows classified as a success (treatment success rate) for reduced inflammation at 6 hours post-treatment in the Banamine® Transdermal group was required to be significantly different ($P < 0.05$) and numerically higher than the treatment success rate for reduced inflammation at 6 hours post-treatment in the dyed saline control group.

**Statistical Methods:** The individual animal was the experimental unit. Treatment success rates for both control of pyrexia and control of inflammation were analyzed using generalized linear mixed models where a binomial distribution was assumed and a logit link was used. Treatment, investigator (site), and investigator (site) by treatment were included as fixed effects and site and site by treatment were included as random effects. The contrast between the success rates of the Banamine® Transdermal-treated group and the saline control group was tested at the two-sided 0.05 significance level.

**Results:** There were a total of eighteen animals and six sites removed from the statistical analysis among the 19 clinical investigators (sites) that enrolled animals because of either protocol deviations (ten animals) or the enrollment of less than four cows by the investigator (eight animals).

A total of 130 cows were included in the statistical analysis (64 in the Banamine® Transdermal group and 66 in the saline control group). The percentage of cows classified as a treatment success for the control of pyrexia

in the Banamine® Transdermal group (61/64, 95%) was statistically significantly different from ($P < 0.0001$) and numerically higher than the percentage of cows classified as a treatment success in the dyed saline control group (23/66, 35%).

The percentage of cows classified as a treatment success for the control of inflammation in the Banamine® Transdermal group (3/64, 4.69%) was not statistically significantly different ($P=0.3298$) from the percentage of cows classified as a treatment success in the dyed saline control group (1/66, 1.52%).

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

**Conclusions:** The results of this study demonstrate that Banamine® Transdermal, when administered once at a dose of 3.3 mg flunixin/kg bw is effective under a variety of environmental conditions for the control of pyrexia associated with acute bovine mastitis.

## III. TARGET ANIMAL SAFETY

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-450 dated July 21, 2017, contains a summary of target animal safety studies and pharmacokinetic information for beef and dairy cattle with the exception of 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.

## IV. HUMAN FOOD SAFETY

### A. Microbial Food Safety

The Agency evaluated the need to address the impact of the use of flunixin on antimicrobial resistance among bacteria of public health concern in or on flunixin-treated cattle. After reviewing information (literature, data, etc.) both submitted by the sponsor and available in the public domain, the Agency determined:

- Flunixin is not regularly considered to have properties that would exert pressure towards the emergence or selection of resistant bacteria of public health concern in food-producing animals,
- Flunixin is not used to treat gastroenteritis or other bacterial diseases in humans,
- Flunixin (or a similar class representative) is not under development to treat a bacterial disease in humans, and
- Flunixin is not indicated for a bacterial disease in a food-producing animal species.

Therefore, the Agency determined there was no need to provide additional microbial food safety (antimicrobial resistance) information or data regarding this approved use of flunixin in cattle.

## B. Toxicology

Reassessment of the codified ADI or safe concentrations was not needed for this supplemental approval. The codified ADI for total residue of flunixin is 0.72 µg/kg of body weight per day, as listed under 21 CFR §556.286. The safe concentrations for total residue of flunixin in individual edible tissues of cattle are 100 parts per billion (ppb) for muscle, 300 ppb for liver, 600 ppb for kidney, and 600 ppb for fat, and 10 ppb for milk. These values reflect the partition of the ADI between meat (70% of the ADI) and milk (30% of the ADI).

The FOI Summary for the supplemental approval of NADA 101-479, dated May 6, 1998, contains summaries of all toxicology studies and information.

## C. 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 supplemental approval. The FOI Summaries for the supplemental approval of NADA 101-479 dated May 6, 1998, and August 19, 2004, contain summaries of total residue and metabolism studies for flunixin in beef cattle 2 months of age and older and dairy cattle.

   b. Comparative Metabolism Study

      CVM did not require comparative metabolism studies for this supplemental approval. The FOI Summaries for the supplemental approval of NADA 101-479 dated May 6, 1998, and August 19, 2004, contain summaries of comparative metabolism studies for flunixin in beef cattle 2 months of age and older and dairy cattle.

   c. Studies to Establish Withdrawal Period and Milk Discard Time

      (1) Tissue Residue Depletion Study

         CVM did not require a tissue residue depletion study for this supplemental approval. The FOI Summary for the approval of NADA 141-450 dated July 21, 2017, contains a summary of the tissue residue depletion study for flunixin in beef cattle 2 months of age and older and dairy cattle.

      (2) Milk Residue Depletion Study

         **Title:** Milk Residue Depletion Study of 5-Hydroxy Flunixin in Dairy Cattle Following Administration of Flunixin Transdermal Solution (Intervet Study Number S16006-00)

         **Study Dates:** June 3, 2020, to March 28, 2022

         **Study Locations:** Manhattan, KS (in-life phase) and Plainsboro, NJ (analytical phase)

Objective: This GLP-study was conducted to measure the concentration of 5-hydroxy flunixin residues in the milk of lactating dairy cattle after a single topical administration of flunixin transdermal solution at 3.3 mg/kg BW.

Study Animals: Twenty-four Holstein dairy cattle weighing 449-694 kg at initiation of the study.

Dose Administration: Animals were group-housed in a single pen and dosed topically on the dorsum along the backbone as a thin line from the withers to the tail head with a single dose of 3.3 mg/kg BW flunixin transdermal solution. Animals were dosed immediately following the AM milk collection on Day 0 (July 22, 2020).

Sampling: Milk samples were collected every 12 hours beginning during the acclimation period and for 7 days following dose administration.

**Milk Assay Results:** The mean results for each time point for the LC-MS/MS assay are provided in Table IV.1. Mean 5-hydroxy flunixin concentrations fell below the codified tolerance of 2 ppb by 36 hours post-dose.

**Table IV.1. LC-MS/MS Assay – Mean Concentrations (ppb) of 5-hydroxy flunixin analyzed at each collection time point.**

| Time post-dose (hours) | Mean ± S.D. |
|---|---|
| 12 | 45.7 ± 14.7 |
| 24 | 9.7 ± 3.6 |
| 36 | 1.6 ± 0.7 |
| 48 | 0.5 ± 0.2 |
| 60 | 0.4 ± 0.2 |
| 72 | 0.3 ± 0.1 |
| 84 | 0.3 ± 0.1 |
| 96 | 0.4 ± 0.4 |
| 108 | 0.3 ± 0.2 |
| 120 | 0.3 ± 0.1 |
| 132 | 0.3 ± 0.1 |
| 144 | 0.3 ± 0.1 |
| 156 | 0.2 ± 0.1 |
| 168 | 0.177 |
| 180 | 0.151 |

LOQ = 0.139 ppb

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 marker residue in milk is 5-hydroxy flunixin.

The studies supporting the target tissue and marker residue assignments can be found under NADA 101-479 FOI Summaries dated May 6, 1998, and August 19, 2004.

3. Tolerances

   Cattle tolerances are 125 ppb flunixin free acid in liver, 25 ppb flunixin free acid in muscle and 2 ppb 5-hydroxy flunixin in milk (21 CFR 556.286). See the FOI Summaries for the supplemental approvals of NADA 101-479 dated May 6, 1998, and August 19, 2004.

4. Withdrawal Period and Milk Discard Time

   This supplement does not result in a change to the previously established withdrawal period. The withdrawal period remains 8 days. Refer to the FOI Summary for the approval of NADA 141-450, dated July 21, 2017.

   Milk residue data from Study No. S16006-00 were analyzed using a statistical tolerance limit algorithm that determines the upper tolerance limit for the 99$^{th}$ percentile of the population with 95% confidence. As *per* guidance, timepoints relevant to the milk tolerance of 2 ppb were used in the analysis (12 hours through 60 hours). The data support assignment of a 48-hour milk discard time when used according to label directions in beef cattle 2 months of age and older and dairy cattle.

### D. Analytical Method for Residues

The FOI Summary for the original approval of NADA 141-450 dated July 21, 2017, contains the analytical method summary for flunixin transdermal solution in cattle liver tissue. Milk residues were measured using the LC-MS/MS official method.

The validated analytical methods for analysis of residues of flunixin transdermal solution are on file at the Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855. To obtain a copy of the analytical methods, please submit a Freedom of Information request to: https://www.accessdata.fda.gov/scripts/foi/FOIRequest/requestinfo.cfm.

## 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 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). 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 order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to provide guidance for the safe and effective use of the product 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. Furthermore, professional expertise is required to monitor the safe use of the product, including treatment of any adverse reactions.

### B. Exclusivity

This supplemental approval for Banamine® Transdermal qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the FD&C Act because the supplemental application included effectiveness studies. This exclusivity begins as of the date of our approval letter and only applies to the new therapeutic indication for the control of pyrexia associated with acute bovine mastitis, and the new target animal subclass of lactating dairy cows.

### C. Supplemental Applications

This supplemental NADA required a reevaluation of the safety or effectiveness data in the original NADA (21 CFR 514.106(b)(2)).

### D. Patent Information

For current information on patents, see the Green Book Reports in the Animal Drugs @ FDA database.