Date of Approval: October 14, 2014

AMENDED ORIGINAL FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-581

FLUNAZINE

(flunixin meglumine)

Paste

Horses

For the alleviation of inflammation and pain associated with musculoskeletal disorders in the horse

Sponsored by:

Cross Vetpharm Group Ltd.

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I. GENERAL INFORMATION:

A. File Number

ANADA 200-581

B. Sponsor

Cross Vetpharm Group Ltd.
Broomhill Rd.
Tallaght, Dublin 24
Ireland

Drug Labeler Code: 061623

US Agent Name and Address:

Ms. Jodi Ann Beaudry
Bimeda Inc.
291 Forest Prairie Rd.
Le Sueur, MN, 56058, US

C. Proprietary Name

FLUNAZINE

D. Established Name

flunixin meglumine

E. Pharmacological Category

Analgesic and non-steroidal anti-inflammatory

F. Dosage Form

Paste

G. Amount of Active Ingredient

30 grams of paste contains flunixin meglumine equivalent to 1,500 mg of flunixin

H. How Supplied

A syringe containing 30 grams of paste

I. Dispensing Status

Rx

J. Dosage Regimen

0.5 mg per pound of body weight per day for up to 5 days

K. Route of Administration

Oral

L. Species/Class

Horses

M. Indication

For the alleviation of inflammation and pain associated with musculoskeletal disorders in the horse.

N. Reference Listed New Animal Drug

BANAMINE; flunixin meglumine; NADA 137-409; Intervet Inc.

II. BIOEQUIVALENCE:

Under the provisions of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act of 1988, an abbreviated new animal drug application (ANADA) may be submitted for a generic version of an approved new animal drug (reference listed new animal drug or RLNAD). New target animal safety and effectiveness data and human food safety data (other than tissue residue data) are not required for approval of an ANADA. Information to show that the generic version is bioequivalent to the approved RLNAD is required for approval.

For this ANADA, an *in vivo* blood-level bioequivalence study was conducted to demonstrate bioequivalence using the generic and RLNAD flunixin meglumine in horses. The strength of the generic and the RLNAD products is the same: 1500 mg flunixin per 30 grams paste per syringe.

A. Bioequivalence Study

The *in vivo* blood-level bioequivalence study data demonstrated the generic product is bioequivalent to the approved RLNAD. The study information is summarized below:

1. Title:

   Comparative Bioavailability Study of Flunixin Meglumine Oral Paste in Horses

2. Testing Facility:

   In-life test facility:

   Southwest Bio-Labs, Inc.
   Las Cruces, NM
   Study number: 009-01080

   Analytical test facility:

   Pharmaceutical Product Development (PPD)
   Middleton, WI
   Project Code: AFJR

3. Objective:

   To evaluate blood-level bioequivalence of the generic flunixin meglumine oral paste (Cross Vetpharm Group Ltd.) in horses compared to BANAMINE Paste (Intervet Inc.), NADA 137-409.

4. Animals:

   12 healthy male horses.

5. Experimental Design:

   The study was conducted as a two-period two-treatment crossover design with a 14-day washout interval between study periods. A third period (following a 14-day washout interval) was added to the design due to an unexpected storage problem that invalidated blood samples collected from period 1. Periods 2 and 3 thus constituted the intended two-treatment crossover design.

6. Treatment:

   In each period, BANAMINE Paste (RLNAD) or the generic flunixin meglumine paste (test article) was orally administered to each animal at a dose of 0.5 mg flunixin (0.01 g paste) per pound of body weight.

7. Measurements and Observations:

   The plasma concentrations of flunixin were measured using a validated bioanalytical method. Pharmacokinetic parameters were determined for each animal individually in each period. General health observations of animals were made twice daily throughout the study. Each animal was observed intermittently for the occurrence of adverse events during the first twelve hours of the dose day of each period.

8. Statistical Methods:

   Blood level bioequivalence was assessed based on measured plasma flunixin concentrations for the area under the curve (AUC) from time 0 to the first value below the lower limit of quantification (LOQ), observed maximum concentration (C_{MAX}) and time of C_{MAX} (T_{MAX}). For analysis, $AUC_{0\text{-}LOQ}$ and C_{MAX} were logarithmically (natural log) transformed to LAUC and LC_{MAX}, respectively. Only the data from periods 2 and 3 were analyzed. A linear mixed effects model containing treatment, sequence, and period as fixed effects, and horse within sequence as a random effect was used to analyze LC_{MAX} and $LAUC_{0\text{-}LOQ}$. Confidence intervals for the ratio of the two treatments were based on back-transforming the endpoints of the 90% confidence interval for the difference between the two treatments for both $LAUC_{0\text{-}LOQ}$ and LC_{MAX}. The endpoints were compared to the acceptance range of 80% to 125% for bioequivalence evaluation. No statistically significant effects (α =0.05) for treatment, sequence or period were detected in the analysis of $LAUC_{0\text{-}LOQ}$ or LC_{MAX}. The following table provides the back transformed results for $AUC_{0\text{-}LOQ}$ and C_{MAX} and the arithmetic means for T_{MAX}. $AUC_{0\text{-}LOQ}$ and C_{MAX} are within the prescribed bounds of 80% to 125%. T_{MAX} values obtained for the test article and RLNAD indicate that these drugs will provide equivalent therapeutic results.

Variable	RLNAD (Intervet, Inc. BANAMINE Paste)	Test (Cross Vetpharm Ltd. flunixin meglumine paste)	Lower Bound	Upper Bound
$AUC_{0\text{-}LOQ}$ (ng/mL)*minute	1,152,910.30‡	1,229,969.59‡	97.18%	117.11%
C_{MAX} (ng/mL)	4,208.24‡	4,259.90‡	88.87%	115.31%
T_{MAX} (minutes)	78.3†	106.7†	NA	NA

‡ Geometric Mean
† Arithmetic Mean

9. Conclusion:

The generic flunixin meglumine paste is bioequivalent to the RLNAD (BANAMINE Paste) for AUC and C_{MAX} when administered orally to horses at a dose of 0.5 mg flunixin per pound of body weight.

B. Bioequivalence Waiver

Not applicable

III. EFFECTIVENESS:

CVM did not require effectiveness studies for this approval.

IV. TARGET ANIMAL SAFETY:

CVM did not require target animal safety studies for this approval.

V. HUMAN FOOD SAFETY:

Data on human food safety, pertaining to drug residues in food, were not required for approval of this application. This drug is approved for use in horses, which are not food producing animals.

VI. USER SAFETY:

CVM did not require user safety studies for this approval.

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

- Do not use in horses intended for human consumption.
- KEEP OUT OF REACH OF CHILDREN
- FOR ORAL USE IN HORSES ONLY

VII. AGENCY CONCLUSIONS:

This information submitted in support of this ANADA satisfies the requirements of section 512(n) of the Federal Food, Drug, and Cosmetic Act and demonstrates that FLUNAZINE, when used according to the label, is safe and effective.