Date of Approval: August 31, 2023

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-757

Acepromazine Maleate Tablets

Dogs

As an aid in tranquilization and as a preanesthetic agent in dogs. Acepromazine Maleate Tablets can be used as an aid in controlling intractable animals during examination, treatment, grooming, x-ray and minor surgical procedures.

Sponsored by:

ZyVet Animal Health, Inc.

Executive Summary

Acepromazine Maleate Tablets are approved as an aid in tranquilization and as a preanesthetic agent in dogs. Acepromazine Maleate Tablets can be used as an aid in controlling intractable animals during examination, treatment, grooming, x-ray and minor surgical procedures. The reference listed new animal drug (RLNAD) is PromAce® Tablets (acepromazine maleate tablets), sponsored by Boehringer Ingelheim Animal Health USA Inc., under NADA 117-532. This is the first generic acepromazine maleate tablets for dogs.

Bioequivalence

The sponsor conducted one *in vivo* blood-level study in dogs to show that the 25 mg Acepromazine Maleate Tablets are bioequivalent to the 25 mg PromAce® Tablets. No serious adverse events were reported during the study.

The sponsor conducted a comparative *in vitro* dissolution study for the additional product strength. Based on the dissolution data, the 10 mg tablet qualified for a waiver from the requirement to perform separate *in vivo* bioequivalence studies (a biowaiver). FDA granted a biowaiver for this strength.

Conclusions

Based on the data submitted by the sponsor for the approval of Acepromazine Maleate Tablets, FDA determined that the drug is safe and effective when used according to the label.

Table of Contents

I. GENERAL INFORMATION

A. File Number

ANADA 200-757

B. Sponsor

ZyVet Animal Health, Inc.
73 Route 31N
Pennington, NJ 08534

Drug Labeler Code: 086117

C. Proprietary Name

Acepromazine Maleate Tablets

D. Drug Product Established Name

acepromazine maleate tablets

E. Pharmacological Category

Tranquilizer

F. Dosage Form

Tablets

G. Amount of Active Ingredient

10 mg and 25 mg tablet sizes

H. How Supplied

10 mg tablets in 100 and 500 count bottles, and 25 mg tablets in 100 and 500 count bottles

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

0.25 – 1.0 mg/lb of body weight. Dosage may be repeated as required.

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indications

As an aid in tranquilization and as a preanesthetic agent in dogs. Acepromazine Maleate Tablets can be used as an aid in controlling intractable animals during examination, treatment, grooming, x-ray and minor surgical procedures.

N. Reference Listed New Animal Drug

PromAce® Tablets; acepromazine maleate tablets; NADA 117-532; Boehringer Ingelheim Animal Health USA Inc.

II. BIOEQUIVALENCE

The Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) of 1988, allows for an abbreviated new animal drug application (ANADA) to be submitted for a generic version of an approved new animal drug (RLNAD). The ANADA sponsor is required to show that the generic product is bioequivalent to the RLNAD, which has been shown to be safe and effective. Effectiveness, target animal safety and human food safety data (other than tissue residue data) are not required for approval of an ANADA. If bioequivalence is demonstrated through a clinical endpoint study in a food-producing animal, then a tissue residue study to establish the withdrawal period for the generic product is also required.

For this ANADA, one *in vivo* blood-level study was conducted to demonstrate product bioequivalence using the generic and RLNAD 25 mg acepromazine maleate tablets. The RLNAD is available in 10 and 25 mg tablet sizes. The *in vivo* blood-level study was conducted in 42 healthy, fasted dogs. The pivotal parameters to evaluate bioequivalence are the observed maximum plasma drug concentration (C_{MAX}) and area under the concentration-time curve (AUC) from time 0 to the last sampling time before the first unquantifiable concentration after C_{MAX}. Bioequivalence was demonstrated between the 25 mg RLNAD PromAce® Tablets (acepromazine maleate tablets) and the 25 mg generic acepromazine maleate tablets by the average bioequivalence approach as described in the Statistical Methods section below. A waiver from the requirement to demonstrate *in vivo* bioequivalence (biowaiver) for the generic 10 mg tablet was requested. Dissolution data was used to demonstrate that the generic 10 mg acepromazine maleate tablets are comparable to the generic 25 mg tablet strength used in the *in vivo* blood-level bioequivalence study. Therefore, a biowaiver for the generic 10 mg acepromazine maleate tablets was granted. The study information is summarized below.

A. Blood-level Bioequivalence Study in Dogs

Title: A Masked, Randomized, Two Period, Two Sequence, Single Oral Dose, Cross-Over, Pivotal Bioequivalence Study of Generic Acepromazine Maleate Tablets USP 25 mg and PromAce® (Acepromazine Maleate) Tablets 25 mg in Healthy Dogs, Under Fasted Conditions. (Study No. 113-BC-2321)

Study Dates: June 6, 2022, to January 4, 2023

Study Locations:

In-life phase: Ontario, Canada

Bioanalytical testing: Ontario, Canada

Study Design:

Objective: The objective of this study was to determine the comparative *in vivo* blood-level bioequivalence data for the generic 25 mg acepromazine maleate tablets and the RLNAD 25 mg PromAce® Tablets (acepromazine maleate tablets) in fasted dogs.

Study Animals: Forty-two male beagle dogs (41 intact males and 1 neutered male) aged 513 – 1,321 days on study day 0 and weighing 9.3 – 12.6 kg on study day -2.

Experimental Design: A randomized, masked, two-period, two-sequence, single-dose crossover study conducted according to Good Laboratory Practice for Nonclinical Laboratory Studies.

Drug Administration: Each animal received 25 mg of either the generic or RLNAD acepromazine maleate tablets according to their randomized treatment sequence (generic/RLNAD or RLNAD/generic).

Measurements and Observations: The plasma concentrations of acepromazine were measured using a validated bioanalytical method. Pharmacokinetic parameters were determined for each animal individually in each period. Animal observations were made throughout the study for assessment of general health and adverse events.

Statistical Methods:

The laboratory study was conducted as a randomized, masked two-period, two-sequence, two-treatment, single-dose crossover design using 42 dogs with a 7-day washout between periods. Appropriate randomization of animal to sequence and pen/treatment order was performed. Primary variables evaluated were C_{MAX} and AUC. Time to maximum concentration (T_{MAX}) was summarized and evaluated clinically.

A mixed-effect model was used to evaluate bioequivalence. The model included fixed effects of treatment, sequence and period, and a random effect of subject nested within sequence. Prior to the analysis, C_{MAX} and AUC were natural logarithm transformed. Bioequivalence is established because the back-transformed estimated upper and lower bounds of the 90% confidence interval for geometric mean ratios (generic:RLNAD) of both C_{MAX} and AUC are contained within the acceptance limits of 0.80 to 1.25.

Results:

As seen in the table below, C_{MAX} and AUC fall within the prescribed bounds (Table II.1). The mean values of T_{MAX} obtained for the generic article and RLNAD were summarized.

Table II.1 Bioequivalence Evaluation

Parameter	Generic Mean	RLNAD Mean	Ratio◊	Lower 90% CI	Upper 90% CI
AUC (ng/mL)*hour	185.0†	187.7†	0.99	0.89	1.09
C_{MAX} (ng/mL)	44.6†	48.1†	0.93	0.80	1.07
T_{MAX} (hours) (SD)‡	1.35 (0.65)‡	1.14 (0.46)‡	NE	NE	NE

RLNAD = PromAce® Tablets (acepromazine maleate tablets); Generic = generic acepromazine maleate tablets
† Geometric mean
‡ Arithmetic mean and standard deviation (SD)
◊ Ratio = Test/Reference
CI = confidence interval
NE = not estimated

Adverse Reactions:

There were no serious adverse events reported during the study.

Conclusion:

The *in vivo* bioequivalence study demonstrated that the generic 25 mg acepromazine maleate tablets and the RLNAD 25 mg PromAce® Tablets (acepromazine maleate tablets) are bioequivalent in dogs.

B. Bioequivalence Waiver

A pivotal *in vivo* blood bioequivalence study was conducted using the 25 mg acepromazine maleate tablet strength. A waiver from the requirement to perform *in vivo* bioequivalence studies (biowaiver) for the generic 10 mg tablet was requested. To qualify for a biowaiver for this product strength, comparative *in vitro* dissolution studies were conducted to determine the dissolution profiles of the generic and RLNAD 25 mg and 10 mg acepromazine maleate tablet strengths. Comparisons were made between the following tablets:

- Generic 25 mg and RLNAD 25 mg tablets
- Generic 25 mg and generic 10 mg tablets
- Generic 10 mg and RLNAD 10 mg tablets

Test conditions were as follows:

- Dissolution apparatus: USP Apparatus II
- Dissolution medium: 0.1 N HCl
- Dissolution medium volume: 900 mL

- Temperature: 37 °C
- Paddle speed: 50 rpm
- Number of vessels: 12
- Data points: 5, 10, 15, 20, 30, and 45 minutes

The generic drug lot number used in the *in vivo* bioequivalence study was the same lot used to support the *in vitro* profile comparisons. Analytical method validation was required to ensure that the quantification of drug concentrations in all samples was accurate and precise.

To allow use of mean data, the percent coefficient of variation at the earlier time points (e.g., 15 minutes) should not be more than 20%, and at other time points should not be more than 10%. The percent coefficient of variation for all generic product profiles was within acceptable limits. Only one measurement should be considered after 85% dissolution of one of the products. If applicable the similarity factor (f_2) should be greater than 50 to ensure sameness or equivalence of two profiles.

Table II.2 Similarity Results

Dissolution Comparison	Similarity Results
25 mg generic to the 25 mg RLNAD	> 85% in 15 minutes
25 mg generic to the 10 mg generic	> 85% in 15 minutes
10 mg generic to the 10 mg RLNAD	> 85% in 15 minutes

Study results demonstrate similar dissolution profiles for all comparisons. Because of rapid dissolution was demonstrated (> 85% in 15 minutes) in all strengths, a dissolution profile comparison using the f_2 test is unnecessary. When comparative profiles between tablets do not require an f_2 test because of rapid dissolution or when the f_2 value is ≥ 50, the product strengths used in the comparison qualify for a biowaiver. Therefore, a biowaiver for the generic 10 mg acepromazine maleate tablet is granted.

III. HUMAN FOOD SAFETY

This drug is intended for use in dogs. Because this new animal drug is not intended for use in food-producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this ANADA.

IV. USER SAFETY

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

Keep out of reach of children.

V. AGENCY CONCLUSIONS

The data submitted in support of this ANADA satisfy the requirements of section 512(c)(2) of the FD&C Act. The data demonstrate that Acepromazine Maleate Tablets, when used according to the label, is safe and effective for the indications listed in Section I.M. above.