Date of Approval: October 29, 2019

# FREEDOM OF INFORMATION SUMMARY

## ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-635

Clomipramine Hydrochloride Tablets

clomipramine hydrochloride

Dogs

Clomipramine Hydrochloride Tablets are to be used as part of a comprehensive behavioral management program to treat separation anxiety in dogs greater than 6 months of age

Sponsored by:

Mizner Bioscience LLC

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# I. GENERAL INFORMATION

## A. File Number

ANADA 200-635

## B. Sponsor

Mizner Bioscience LLC
225 NE Mizner Blvd., Suite 760
Boca Raton, FL 33432

Drug Labeler Code: 086039

## C. Proprietary Name

Clomipramine Hydrochloride Tablets

## D. Drug Product Established Name

clomipramine hydrochloride

## E. Pharmacological Category

Tricyclic antidepressant

## F. Dosage Form

Tablets

## G. Amount of Active Ingredient

5 mg, 20 mg, 40 mg, and 80 mg.

## H. How Supplied

Clomipramine Hydrochloride Tablets are scored and available in 5, 20, 40 and 80 mg tablet strengths. Each tablet strength is packaged in color-coded bottles containing 30 scored tablets.

## I. Dispensing Status

Rx

## J. Dosage Regimen

The recommended daily dose of Clomipramine Hydrochloride Tablets is 2 to 4 mg/kg/day (0.9 – 1.8 mg/lb/day) (see dosing table below). It can be administered as a single daily dose or divided twice daily based on patient response and/or tolerance of the side effects. It may be prudent to initiate treatment in divided doses to minimize side effects by permitting tolerance to side effects to develop or allowing the patient time to adapt if tolerance does not develop. To reduce the incidence of vomiting that may be experienced by some dogs, Clomipramine Hydrochloride Tablets may be given with a small amount of food. If a dose is

missed, the next dose should be administered (without doubling) at the next scheduled dosing time.

| Dog Weight (lbs.) | Clomipramine Hydrochloride per Day | No. Tablets per Day | Tablet Strength |
|---|---|---|---|
| 2.75-5.5 | 5 mg | 1 | 5 mg |
| 5.6-10.9 | 10 mg | 2 | 5 mg |
| 11-22 | 20 mg | 1 | 20 mg |
| 22.1-44 | 40 mg | 1 | 40 mg |
| 44.1-88 | 80 mg | 1 | 80 mg |
| 88.1-176 | 160 mg | 2 | 80 mg |

Once the desired clinical effect is achieved and the owners have successfully instituted the appropriate behavioral modification, the dose of Clomipramine Hydrochloride Tablets may be reduced to maintain the desired effect or discontinued.

**K. Route of Administration**

Oral

**L. Species/Class**

Dogs

**M. Indication**

Clomipramine Hydrochloride Tablets are to be used as part of a comprehensive behavioral management program to treat separation anxiety in dogs greater than 6 months of age.

**N. Reference Listed New Animal Drug**

Clomicalm™; clomipramine hydrochloride; NADA 141-120; Elanco US 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. 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 certain dosage forms, the agency will grant a waiver from the requirement to perform *in vivo* bioequivalence studies (biowaiver) (55 FR 24645, June 18, 1990; Fifth GADPTRA Policy Letter; Bioequivalence Guideline, October 9, 2002).

For this ANADA, one *in vivo* blood-level study was conducted to demonstrate product bioequivalence using the generic and RLNAD clomipramine hydrochloride 20 mg tablet. The RLNAD is available in 5, 20, 40, and 80 mg tablet sizes. The *in vivo* blood-level study was conducted in 28 healthy, fed dogs; however, one animal was removed from the study because of a dosing failure. Bioequivalence was demonstrated between the 20 mg RLNAD clomipramine hydrochloride tablet and the 20 mg generic clomipramine hydrochloride tablet by demonstrating that the confidence limits for the difference between the pivotal parameters $C_{MAX}$ and AUC are contained within the equivalence limits of 80.00% and 125.00%. A waiver from the requirement to demonstrate *in vivo* bioequivalence (biowaiver) for the generic 5 mg, 40 mg, and 80 mg tablets was requested. Dissolution data was used to demonstrate that the generic 5 mg, 40 mg, and 80 mg clomipramine hydrochloride tablets are comparable to the generic 20 mg tablet strength used in the *in vivo* blood-level bioequivalence study. Therefore, a biowaiver for the generic 5 mg, 40 mg and 80 mg clomipramine hydrochloride tablets was granted. The study information is summarized below.

## A. Canine Blood-Level Bioequivalence Study

One blood-level bioequivalence study was conducted to determine the comparative bioavailability of the generic and RLNAD formulations of clomipramine hydrochloride tablets (20 mg).

1. Study Title:
   Two-way Oral Bioequivalence Study of Two Clomipramine HCL Preparations in Dogs

2. Protocol:
   A randomized, two-period, two-sequence, single-dose crossover study to evaluate the relative bioavailability of a generic 20 mg clomipramine hydrochloride tablet compared to the RLNAD 20 mg CLOMICALM® (clomipramine hydrochloride) tablet (Elanco US, Inc., NADA 141-120) in 28 fed, healthy female beagle dogs.

3. Testing Facilities:
   In-life test phase: Southwest Bio-Labs, Inc.,
   Las Cruces, NM 88005

   Bioanalytical testing: Pyxant Labs Inc.,
   Colorado Springs, CO 80907

4. Study Number:
   Southwest Bio-Labs, Inc. (SBL): 016-01534

5. Objective:
   The objective of this study was to determine the comparative *in vivo* blood level bioequivalence of Mizner Bioscience, LLC's 20 mg generic clomipramine hydrochloride tablets and Elanco US, Inc.'s 20 mg CLOMICALM® (clomipramine hydrochloride) tablets in a randomized, two period, two-sequence, single-dose crossover study in dogs.

6. Measurement and Observation:

The plasma concentrations of clomipramine 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. One animal was excluded from the study due to dosing failure.

7. Statistical Methods:
The study was conducted as a randomized, two-period, two-sequence, single-dose crossover design using 28 dogs with a 21 day washout between periods. The randomization to sequence and pen number/treatment order assignments were generated using a Statistical Analysis System (SAS) program. Primary variables evaluated are area under the curve from time 0 to the first observed concentration below the limit of quantitation (AUC) and maximum concentration ($C_{MAX}$). Time to maximum concentration ($T_{MAX}$) is also evaluated. The statistical model included sequence, treatment, and period as fixed effects, and animal-within-sequence as a random effect.

The criteria for determining bioequivalence is to construct a 90% confidence interval about the difference of the two means, generic minus RLNAD, based on the natural log scale of AUC and $C_{MAX}$ and then take the anti-log of the confidence limits multiplied by 100. To demonstrate bioequivalence, the resulting bounds should be between 80.00% and 125.00% for both AUC and $C_{MAX.}$ As seen in the table below, AUC and $C_{MAX}$ fall within the prescribed bounds (Table II.1). $T_{MAX}$ values obtained for the test product and reference product indicate that these drugs will provide equivalent therapeutic results.

**Table II.1: Bioequivalence Evaluation**

| **Parameter** | **Test** | **Reference** | **Ratio*** | **Ratio Lower Bound** | **Ratio Upper Bound** |
|---|---|---|---|---|---|
| AUC (min*ng/mL) | 55855† | 55315† | 1.01 | 90 | 113 |
| $C_{MAX}$ (ng/mL) | 217† | 224† | 0.97 | 82 | 114 |
| $T_{MAX}$ (min) | 89.26‡ | 91.11‡ | NE | NE | NE |

* Ratio = Test/Reference
† Geometric mean
‡ Arithmetic mean
NE = not estimated

## B. Bioequivalence Waiver

A pivotal *in vivo* blood bioequivalence study was conducted using the 20 mg clomipramine hydrochloride tablet strength. A waiver from the requirement to perform *in vivo* bioequivalence studies (biowaiver) for the generic 5 mg, 40 mg, and 80 mg tablets was requested. To qualify for a biowaiver for each of these product strengths, comparative *in vitro* dissolution studies were conducted to determine the dissolution profiles of Mizner Bioscience LLC's generic 5 mg, 20 mg, 40 mg, and 80 mg clomipramine hydrochloride tablets.

Test conditions were as follows:
- Dissolution apparatus: USP Apparatus II (Paddles)
- Dissolution medium: 0.1 N hydrochloric acid

- Dissolution medium volume: 500 mL
- Temperature: 37.0 ±0.5 °C
- Paddle speed: 50 rpm
- Number of vessels: 12
- Data points: 5, 15, 30, 45, 60 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.

All tablet strengths achieved at least 85% dissolution within 15 minutes. CVM considers tablets that achieve 85% dissolution within 15 minutes to have similar dissolution profiles and does not require additional analysis such as the f2 metric to demonstrate similarity. These study results demonstrate similar dissolution profiles for all comparisons. Therefore, a biowaiver for the generic 5 mg, 40 mg and 80 mg clomipramine hydrochloride tablets 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 Clomipramine Hydrochloride Tablets:

Not for use in humans. Keep out of reach of children. In case of accidental ingestion seek medical attention immediately. In children, accidental ingestion should be regarded as serious. There is no specific antidote for clomipramine. Overdose in humans causes anticholinergic effects including effects on the central nervous (e.g., convulsions) and cardiovascular (e.g., arrhythmia, tachycardia) systems. People with known hypersensitivity to clomipramine should administer the product with caution. In case of accidental human ingestion, call 1-561-570-1875.

## V. AGENCY CONCLUSIONS

This information submitted in support of this ANADA satisfy the requirements of section 512(c)(2) of the Federal Food, Drug, and Cosmetic Act. The data demonstrate that Clomipramine Hydrochloride Tablets when used according to the label, is safe and effective.