Date of Approval: October 21, 2025

FREEDOM OF INFORMATION (FOI) SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION (ANADA)

ANADA 200-825

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:

Felix Pharmaceuticals Pvt. Ltd.

Executive Summary

Clomipramine Hydrochloride Tablets are approved to be used as part of a comprehensive behavioral management program to treat separation anxiety in dogs greater than 6 months of age. The reference listed new animal drug (RLNAD) is CLOMICALM® (clomipramine hydrochloride) tablets sponsored by Virbac AH, Inc. under NADA 141-120.

Bioequivalence

The sponsor conducted one *in vivo* blood-level study in dogs to show that the 20 mg strength of Clomipramine Hydrochloride Tablets is bioequivalent to the 20 mg strength of Clomicalm® (clomipramine hydrochloride). No serious adverse events were reported during the study.

The sponsor conducted a comparative *in vitro* dissolution study for the additional product strengths. Based on the dissolution data, the 5, 40, and 80 mg tablets qualified for a waiver from the requirement to perform separate *in vivo* bioequivalence studies (a biowaiver). FDA granted a biowaiver for these strengths.

Conclusions

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

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I. GENERAL INFORMATION

A. File Number

ANADA 200-825

B. Sponsor

Felix Pharmaceuticals Pvt. Ltd.,
25-28 North Wall Quay
Dublin 1, Ireland

Drug Labeler Code: 086101

U.S. Agent Name and Address:

Sreejith Kurup
Felixvet Inc.
1300 NW Briarcliff Parkway
Suite 100
Kansas City, MO 64150

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 available in 5 mg, 20 mg, 40 mg, and 80 mg tablet strengths in color-coded packaging for oral administration to dogs.

I. Dispensing Status

Prescription (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.

Dog Weight (lbs.)	Clomipramine Hydrochloride Tablets 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. Withdrawal side effects were not reported in studies with clomipramine hydrochloride tablets in dogs. However, in clinical practice, it is recommended to taper the individual patient dose while continuing to monitor the dog's behavior and clinical status through the dose reduction or withdrawal period.

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; Virbac AH, 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 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 tablets. The RLNAD is available in 5 mg, 20 mg, 40 mg, and 80 mg tablets. The *in vivo* blood-level study was conducted in 30 healthy, fed 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 20 mg RLNAD clomipramine hydrochloride tablets and the 20 mg generic clomipramine hydrochloride tablets by the average bioequivalence approach as described in the Statistical Method section below. A waiver from the requirement to demonstrate *in vivo* bioequivalence (biowaiver) for the generic 5 mg, 40 mg, and 80 mg tablet strengths 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. Blood-level Bioequivalence Study in Dogs

Title: Pivotal Bioequivalence Study of CLOMICALM® Tablets and a Formulation of Generic Clomipramine Hydrochloride Tablets when Administered Orally to Dogs in a Fed State. (Study No. CLMH-KC2-9423)

Study Dates: August 23, 2023 to February 20, 2024

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 20 mg Clomipramine Hydrochloride Tablets (clomipramine hydrochloride) and the RLNAD 20 mg CLOMICALM® (clomipramine hydrochloride) tablets in fed dogs.

Study Animals: Thirty intact dogs between 357 days to 1619 days of age on study day 0 and weighing 9.7 kg to 12.2 kg (when weight was measured on study day -4).

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 40 mg (two 20 mg tablets) of either the generic or RLNAD clomipramine hydrochloride according to their randomized treatment sequence (generic/RLNAD or RLNAD/generic).

Measurements and Observations: The plasma concentrations of clomipramine hydrochloride 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 Method:

The laboratory study was conducted as a randomized, masked two-period, two-sequence, two-treatment, single-dose crossover design using 30 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	614.3[†]	566.5[†]	1.08	1.0	1.17
C_{MAX} (ng/mL)	156.4[†]	153.6[†]	1.02	0.90	1.16
T_{MAX} (hours) (SD)[‡]	1.5 (0.84)[‡]	1.4 (0.51)[‡]	NE	NE	NE

RLNAD = CLOMICALM® Tablets (clomipramine hydrochloride); Generic = generic clomipramine hydrochloride
[†] 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 20 mg clomipramine hydrochloride tablets and the RLNAD 20 mg CLOMICALM® (clomipramine hydrochloride) tablets are bioequivalent in dogs.

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 the generic 5 mg, 40 mg, and 80 mg clomipramine hydrochloride tablets. Comparisons were made between the following tablets:
• Generic 5 mg and generic 20 mg tablets
• Generic 40 mg and generic 20 mg tablets
• Generic 80 mg and generic 20 mg tablets

The objective was to satisfy the similarity factor (f_2) criteria between the generic 20 mg tablet strength and the generic 5 mg, 40 mg, and 80 mg tablet strengths.

Test conditions were as follows:
• Dissolution apparatus: USP Apparatus II
• Dissolution medium: 0.1 N HCl
• Dissolution medium volume: 500 mL
• Temperature: 37°C ± 0.5°C
• Paddle speed: 75 rpm
• Number of vessels: 12
• Data points: 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. Additional comparative dissolution tests were performed using new 5 mg, 20 mg, 40 mg, and 80 mg strength batches, which is acceptable because of the rapidly dissolving characteristics in all strengths. 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. The f_2 value should be greater than 50 to ensure sameness or equivalence of two profiles.

Study results demonstrate similar dissolution profiles for all comparisons. However, because of rapid dissolving characteristics (>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 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:

Human Warnings:
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.

Keep Clomipramine Hydrochloride Tablets in a secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

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 Clomipramine Hydrochloride Tablets, when used according to the label, is safe and effective for the conditions of use in the General Information Section above.