

Date of Approval: June 20, 2024

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-784

Trimeprazine with Prednisolone

Tablets

Dogs

Antipruritic: Trimeprazine with Prednisolone is recommended for the relief of itching regardless of cause. Its usefulness has been demonstrated for the relief of itching and the reduction of inflammation commonly associated with most skin disorders of dogs such as the eczema caused by internal disorders, otitis, and dermatitis (allergic, parasitic, pustular, and nonspecific). It often relieves pruritis which does not respond to other therapy.

Antitussive: Trimeprazine with Prednisolone has been found to be effective therapy and adjunctive therapy in various cough conditions of dogs. Therefore, in addition to its antipruritic action, Trimeprazine with Prednisolone is recommended for the treatment of “kennel cough” or tracheobronchitis, bronchitis including all allergic bronchitis, and infections and coughs of nonspecific origin. (Coughs due to cardiac insufficiency would not be expected to respond to Trimeprazine with Prednisolone therapy).

Sponsored by:

ZyVet Animal Health, Inc.

Executive Summary

Trimeprazine with Prednisolone tablets are approved for the following indications in dogs:

Antipruritic: Trimeprazine with Prednisolone is recommended for the relief of itching regardless of cause. Its usefulness has been demonstrated for the relief of itching and the reduction of inflammation commonly associated with most skin disorders of dogs such as the eczema caused by internal disorders, otitis, and dermatitis (allergic, parasitic, pustular, and nonspecific). It often relieves pruritis which does not respond to other therapy.

Antitussive: Trimeprazine with Prednisolone has been found to be effective therapy and adjunctive therapy in various cough conditions of dogs. Therefore, in addition to its antipruritic action, Trimeprazine with Prednisolone is recommended for the treatment of “kennel cough” or tracheobronchitis, bronchitis including all allergic bronchitis, and infections and coughs of nonspecific origin. (Coughs due to cardiac insufficiency would not be expected to respond to Trimeprazine with Prednisolone therapy).

The reference listed new animal drug (RLNAD) is Temaril-P® (trimeprazine with prednisolone) tablets, sponsored by Zoetis Inc., under NADA 012-437. This is the first generic trimeprazine with prednisolone tablets for dogs.

Bioequivalence

The sponsor conducted one *in vivo* blood-level study in dogs to show that the Trimeprazine with Prednisolone (5 mg trimeprazine with 2 mg prednisolone) tablets are bioequivalent to the Temaril-P® (5 mg trimeprazine with 2 mg prednisolone) tablets. No serious adverse events were reported during the study.

Conclusions

Based on the data submitted by the sponsor for the approval of Trimeprazine with Prednisolone, the Food and Drug Administration (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 200-784

B. Sponsor

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

Drug Labeler Code: 086117

C. Proprietary Name

Trimeprazine with Prednisolone

D. Drug Product Established Name

trimeprazine with prednisolone

E. Pharmacological Category

Antihistamine and corticosteroid

F. Dosage Form

Tablets

G. Amount of Active Ingredient

Each tablet contains 5 mg trimeprazine as trimeprazine tartrate and 2 mg prednisolone.

H. How Supplied

100 and 1000 tablet count bottles

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

The same dosage schedule may be followed for both antipruritic and antitussive therapy.

Weight of Dog	Initial Dosage
Up to 10 lb	½ tablet, twice daily
11 – 20 lb	1 tablet, twice daily
21 – 40 lb	2 tablets, twice daily
Over 40 lb	3 tablets, twice daily

After 4 days, reduce dosage to ½ of the initial dose or to an amount just sufficient to maintain remission of symptoms. Individual animal response will vary and dosage should be adjusted until proper response is obtained.

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indications

Antipruritic: Trimeprazine with Prednisolone is recommended for the relief of itching regardless of cause. Its usefulness has been demonstrated for the relief of itching and the reduction of inflammation commonly associated with most skin disorders of dogs such as the eczema caused by internal disorders, otitis, and dermatitis (allergic, parasitic, pustular, and nonspecific). It often relieves pruritis which does not respond to other therapy.

Antitussive: Trimeprazine with Prednisolone has been found to be effective therapy and adjunctive therapy in various cough conditions of dogs. Therefore, in addition to its antipruritic action, Trimeprazine with Prednisolone is recommended for the treatment of “kennel cough” or tracheobronchitis, bronchitis including all allergic bronchitis, and infections and coughs of nonspecific origin. (Coughs due to cardiac insufficiency would not be expected to respond to Trimeprazine with Prednisolone therapy).

N. Reference Listed New Animal Drug

Temaril-P®; trimeprazine with prednisolone; NADA 012-437; Zoetis 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 5 mg trimeprazine with 2 mg prednisolone tablets. The RLNAD is available in a 5 mg trimeprazine with 2 mg prednisolone tablet size. The *in vivo* blood-level study was conducted in 28 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 RLNAD 5 mg trimeprazine with 2 mg

prednisolone tablets and the generic 5 mg trimeprazine with 2 mg prednisolone tablets by the mixed reference-scaled average bioequivalence approach for trimeprazine and by the average bioequivalence approach for prednisolone as described in the Statistical Methods section below. The study information is summarized below.

A. Blood-level Bioequivalence Study in Dogs

Title: A Masked, Randomized, Four Period, Two Sequence, Single Oral Dose, Cross Over, Pivotal Bioequivalence Study of Trimeprazine (5 mg) with Prednisolone (2 mg) Tablets Versus Temaril-P® Tablets (Trimeprazine 5 mg with Prednisolone 2 mg) in Healthy Dogs, Under Fasted Conditions. (Study No. 113-BC-3422)

Study Dates: February 27, 2023, to October 10, 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 Trimeprazine with Prednisolone tablets, containing 5 mg trimeprazine and 2 mg prednisolone, and the RLNAD Temaril-P® (trimeprazine with prednisolone) tablets, containing 5 mg trimeprazine and 2 mg prednisolone, in fasted dogs.

Study Animals: Twenty-eight intact male and female dogs, aged 416 to 1,391 days on study day 0 and weighing 7.1 to 9.3 kg on study day -2.

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

Drug Administration: Each animal received 5 mg trimeprazine with 2 mg prednisolone of either the generic or RLNAD trimeprazine with prednisolone tablets according to their randomized treatment sequence (generic/RLNAD/generic/RLNAD or RLNAD/generic/RLNAD/generic).

Measurements and Observations: The plasma concentrations of trimeprazine and prednisolone 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, four-period, two-sequence, two-treatment, single-dose crossover design using 28 dogs with a 14-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.

The two analytes, trimeprazine and prednisolone, were analyzed separately.

For the analyte trimeprazine, the reference-scaled average bioequivalence (RSABE) method was used as appropriate to evaluate bioequivalence through the mixed scaling approach. Prior to the analysis, C_{MAX} and AUC values were natural logarithm transformed. The estimated within-subject standard deviation (s_{WR}) of the RLNAD was calculated separately for transformed C_{MAX} and AUC to select the appropriate analysis approach based on FDA Guidances.

- The s_{WR} was equal to or greater than 0.294 for both C_{MAX} and AUC, so the RSABE method was used, and bioequivalence was established based on the following two criteria:
 - The estimated 95 percent upper confidence bound for $(\mu_T - \mu_R)^2 - \theta^* \sigma^2_{WR}$ is less than zero (0), where μ_T and μ_R are the population means of the natural log transformed primary variable for the generic article and RLNAD, respectively, and σ^2_{WR} is the population within-subject standard deviation of log transformed pharmacokinetic parameter values for the RLNAD, $\theta = (\log(1.25)/\sigma_{w0})^2$ and $\sigma_{w0} = 0.25$.
 - The point estimate of the generic to RLNAD geometric mean ratio is contained within the acceptance limits of 0.80 and 1.25.

For the analyte prednisolone, a mixed-effect model was used to evaluate bioequivalence. The statistical model included fixed effects of treatment, sequence and period, and a random effect of subject nested within sequence. Period was modeled as a repeated factor. 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 percent 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 for trimeprazine, C_{MAX} and AUC meet the pre-specified criteria for bioequivalence (Table II.1). The mean values of T_{MAX} obtained for the generic article and RLNAD were summarized.

Table II.1. Bioequivalence Evaluation for Trimeprazine

Parameter	s _{WR}	Generic Mean	RLNAD Mean	Ratio [◊]	95% Upper Bound [§]	90% CI for the Ratio
AUC (ng/mL)*hour	0.3780	6.61 [†]	6.51 [†]	1.04	-0.0701	NE
C _{MAX} (ng/mL)	0.4721	2.44 [†]	2.25 [†]	1.13	-0.0660	NE
T _{MAX} (hours) (SD) [‡]	NE	0.74 (0.51) [‡]	0.77 (0.54) [‡]	NE	NE	NE

[†] Geometric mean

‡ Arithmetic mean and standard deviation (SD)
◊ Ratio = Generic/RLNAD
§ 95% upper confidence bound for $(\mu_T - \mu_R)^2 - \theta^* \sigma^2_{WR}$
CI = confidence interval
NE = not estimated

As seen in the table below for prednisolone, C_{MAX} and AUC fall within the prescribed bounds (Table II.2). The mean values of T_{MAX} obtained for the generic article and RLNAD were summarized.

Table II.2. Bioequivalence Evaluation for Prednisolone

Parameter	Generic Mean	RLNAD Mean	Ratio [◊]	Lower 90% CI	Upper 90% CI
AUC (ng/mL)*hour	332.5 [†]	352.9 [†]	0.94	0.81	1.10
C _{MAX} (ng/mL)	164.2 [†]	163.0 [†]	1.01	0.85	1.19
T _{MAX} (hours) (SD) [‡]	0.75 (0.49) [‡]	0.74 (0.57) [‡]	NE	NE	NE

† Geometric mean
‡ Arithmetic mean and standard deviation (SD)
◊ Ratio = Generic/RLNAD
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 Trimeprazine with Prednisolone tablets, containing 5 mg trimeprazine and 2 mg prednisolone, and the RLNAD Temaril-P[®] (trimeprazine with prednisolone) tablets, containing 5 mg trimeprazine and 2 mg prednisolone, are bioequivalent in dogs.

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, the Center for Veterinary Medicine 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 Trimeprazine with Prednisolone:

None

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 Trimeprazine with Prednisolone, when used according to the label, is safe and effective for the conditions of use in the General Information Section above.