Date of Approval: November 18, 2024

FREEDOM OF INFORMATION (FOI) SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION (ANADA)

ANADA 200-793

PropofolVet Multidose

(propofol injectable emulsion)

Dogs

For induction of anesthesia.
For maintenance of general anesthesia by intermittent bolus injections for short procedures.
For induction of general anesthesia where maintenance is provided by inhalant anesthetics.

Sponsored by:

Parnell Technologies Pty. Ltd.

Executive Summary

PropofolVet Multidose (propofol injectable emulsion) is approved for induction of anesthesia, for maintenance of general anesthesia by intermittent bolus injections for short procedures, and for induction of general anesthesia where maintenance is provided by inhalant anesthetics. The reference listed new animal drug (RLNAD) is PropoFlo™ 28 (propofol injectable emulsion) sponsored by Zoetis Inc. under NADA 141-098. This is the first generic propofol injectable emulsion for dogs.

Bioequivalence

The sponsor conducted one *in vivo* blood-level study in dogs to show that the 10 mg/mL PropofolVet Multidose is bioequivalent to the 10 mg/mL PropoFlo™ 28. No serious adverse events were reported during the study.

Conclusions

Based on the data submitted by the sponsor for the approval of PropofolVet Multidose, the Food and Drug Administration determined that the drug is safe and effective when used according to the label.

Table of Contents

I. GENERAL INFORMATION

A. File Number

ANADA 200-793

B. Sponsor

Parnell Technologies Pty. Ltd.
unit 4, 476 Gardeners Rd.
Alexandria, New South Wales 2015, Australia

Drug Labeler Code: 068504

C. Proprietary Name

PropofolVet Multidose

D. Drug Product Established Name

propofol injectable emulsion

E. Pharmacological Category

Intravenous anesthetic

F. Dosage Form

Injectable emulsion

G. Amount of Active Ingredient

10 mg/mL propofol

H. How Supplied

20 mL multidose vials

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

INDUCTION OF GENERAL ANESTHESIA:

For induction, PropofolVet Multidose should be titrated against the response of the patient over 60 to 90 seconds or until clinical signs show the onset of anesthesia. Rapid injection of propofol (≤5 seconds) may be associated with an increased incidence of apnea. The average preserved propofol injectable emulsion induction dose rates for healthy dogs given propofol alone, or when propofol is preceded by a preanesthetic, are indicated in the table below. This table is based on field study results and is for guidance only. The dose and rate for propofol should be based upon patient response.

Induction Dosage Guidelines				
Preanesthetic*	Propofol Induction Dose	Propofol Rate of Administration		
	mg/kg	Seconds	mg/kg/min	mL/kg/min
None	7.6	60 to 90	5.0 to 7.6	0.50 to 0.76
Benzodiazepine/Opioid	4.7	60 to 90	3.1 to 4.7	0.31 to 0.47
Phenothiazine/Opioid	4.0	60 to 90	2.7 to 4.0	0.27 to 0.40
Alpha$_2$-agonist/Opioid	3.2	60 to 90	2.1 to 3.2	0.21 to 0.32

*Doses for preanesthetics may be lower than the label directions for their use as a single medication.

The use of preanesthetics markedly reduces propofol requirements. Induction dose sparing was approximately 38% with benzodiazepine/opioid preanesthesia, 47% when dogs were preanesthetized with phenothiazine/opioid, and 58% when dogs were preanesthetized with alpha$_2$-agonist. As with other sedative hypnotic agents, the amount of opioid and/or alpha$_2$-agonist premedication will influence the response of the patient to an induction dose of propofol. In the presence of preanesthesia, the dose of propofol may be reduced with increasing age of the animal. The dose of propofol should always be titrated against the response of the patient. During induction, additional low doses of propofol, similar to those used for maintenance with propofol, may be administered to facilitate intubation or the transition to inhalant maintenance anesthesia.

MAINTENANCE OF GENERAL ANESTHESIA:

- Intermittent Propofol Injections:
  Anesthesia can be maintained by administering PropofolVet Multidose in intermittent intravenous (IV) injections. Clinical response will be determined by the amount and the frequency of maintenance injections. The following table is based on field study results and is provided for guidance:

Maintenance Dosage Guidelines				
Preanesthetic*	Propofol Maintenance Dose	Propofol Rate of Administration		
	mg/kg	Seconds	mg/kg/min	mL/kg/min
None	3.2	60	3.2	0.32
Benzodiazepine/Opioid	1.7	60	1.7	0.17
Phenothiazine/Opioid	2.0	60	2.0	0.20

*Doses for preanesthetics may be lower than the label directions for their use as a single medication.

Maintenance dose sparing was approximately 48% with benzodiazepine/opioid preanesthesia and 37% when dogs were preanesthetized with phenothiazine/opioid. Repeated maintenance doses of propofol do not result in increased recovery times or dosing intervals, indicating that the anesthetic effects of propofol are not cumulative.

- Maintenance by Inhalant Anesthetics:
  Due to the rapid metabolism of propofol, additional low doses of propofol, similar to those used for maintenance with propofol, may be required to complete the transition to inhalant maintenance anesthesia. Clinical trials using propofol have shown that it may be necessary to use a higher initial concentration of the inhalant anesthetic halothane than is usually required following induction using barbiturate anesthetics, due to rapid recovery from propofol.

K. Route of Administration

Intravenous

L. Species

Dogs

M. Indications

For induction of anesthesia.
For maintenance of general anesthesia by intermittent bolus injections for short procedures.
For induction of general anesthesia where maintenance is provided by inhalant anesthetics.

N. Reference Listed New Animal Drug

PropoFlo™ 28; propofol injectable emulsion; NADA 141-098; 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 (propofol injectable emulsion) 10 mg/mL products. The RLNAD is available in a 10 mg/mL injectable emulsion strength. The *in vivo*

blood-level study was conducted in 22 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 1 minute following injection to the last sampling time before the first unquantifiable concentration after C_{MAX}. Bioequivalence was demonstrated between the 10 mg/mL RLNAD (propofol injectable emulsion) and the 10 mg/mL generic (propofol injectable emulsion) by the average bioequivalence approach as described in the Statistical Methods section below. The study information is summarized below.

Blood-level Bioequivalence Study in Dogs

Title: Pivotal Bioequivalence Study of PropoFlo™ 28 (Propofol) and Generic Propofol Injectable Emulsion Upon IV Administration to Beagle Dogs. (Study No. 116-BC-0521)

Study Dates: August 8, 2022 to January 11, 2023

Study Locations:

In-life phase: Ontario, Canada

Bioanalytical testing: Somerset, NJ

Study Design:

Objective: The objective of this study was to determine the comparative *in vivo* blood-level bioequivalence data for the generic 10 mg/mL propofol injectable emulsion and the RLNAD 10 mg/mL of PropoFlo™ 28 (propofol injectable emulsion) in fasted dogs.

Study Animals: Twenty-two intact male beagles aged 273 to 1825 days on study day 0 and weighing 9.8 to 12.4 kg on study day -1.

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 7.6 mg/kg of either the generic or RLNAD propofol injectable emulsion according to their randomized treatment sequence (generic/RLNAD or RLNAD/generic).

Measurements and Observations: The plasma concentrations of propofol 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 22 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	1757.89†	1766.65†	1.00	0.96	1.03
C_{MAX} (ng/mL)	10159.63†	9728.37†	1.04	0.97	1.12
T_{MAX} (min) (SD)‡	1.02 (0.05)‡	1.05 (0.17)‡	NE	NE	NE

† Geometric mean
‡ Arithmetic mean and standard deviation (SD)
◊ Ratio = Generic/RLNAD
CI = confidence interval
NE = not estimated
^AUC was estimated from time 1 (1 minute post-dose)

Adverse Reactions:

There were no serious adverse events reported during the study.

Conclusion:

The *in vivo* bioequivalence study demonstrated that the generic 10 mg/mL propofol injectable emulsion and the RLNAD 10 mg/mL PropoFlo™ 28 (propofol injectable emulsion) 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 PropofolVet Multidose:

Not for use in humans. Keep out of the reach of children.

Rare cases of self-administration have been reported, including fatalities. PropofolVet Multidose should be managed to prevent the risk of diversion, through such measures as restriction of access and the use of drug accountability procedures appropriate to the

clinical setting. Exercise caution to avoid accidental self-injection. Overdose is likely to cause cardiorespiratory depression (such as hypotension, bradycardia and/or apnea). Remove the individual from the source of exposure and seek medical attention. Respiratory depression should be treated by artificial ventilation and oxygen. Hypersensitivity reactions to propofol, including anaphylaxis, may occur in some individuals who are also allergic to muscle relaxants. Avoid inhalation and direct contact of this product with skin, eyes, and clothes. In case of contact, eyes and skin should be liberally flushed with water for 15 minutes. Consult a physician if irritation persists.

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