

Approval Date: February 4, 2011

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-098

PROPOFLO 28

Propofol
Injectable Anesthetic
Dogs

The effect of the supplement is to add a preservative (benzyl alcohol) for a multidose presentation in a 20 mL vial

Sponsored by:

Abbott Laboratories

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I. GENERAL INFORMATION:

- A. File Number:** NADA 141-098
- B. Sponsor:** Abbott Laboratories
North Chicago, IL 60064

Drug Labeler Code: 000074
- C. Proprietary Name:** PROPOFLO 28
- D. Established Name:** Propofol
- E. Pharmacological Category:** Intravenous anesthetic
- F. Dosage Form:** Injectable emulsion
- G. Amount of Active Ingredient:** 10 mg propofol/mL
- H. How Supplied:** 20 mL multidose vials
- I. How Dispensed:** Rx

J. Dosage:**INDUCTION OF GENERAL ANESTHESIA:**

For induction, PROPOFLO 28 injection should be titrated against the response of the patient over 60-90 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 PROPOFLO 28 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	60-90	5.0-7.6	0.50-0.76
Benzodiazepine/ opioid	4.7	60-90	3.1-4.7	0.31-0.47
Phenothiazine/ opioid	4.0	60-90	2.7-4.0	0.27-0.40
Alpha ₂ -agonist/ opioid	3.2	60-90	2.1-3.2	0.21-0.32

*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 alpha₂-agonist. As with other sedative hypnotic agents, the amount of opioid and/or alpha₂-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:**A. Intermittent Propofol Injections:**

Anesthesia can be maintained by administering PROPOFLO 28 in intermittent 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		
		seconds	mg/kg/min	mL/kg/min
None	3.22	60	3.2	0.32
Benzodiazepine/ opioid	1.67	60	1.7	0.17
Phenothiazine/ opioid	2.03	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.

B. 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 propofol⁵.

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. Effect(s) of Supplement: The effect of the supplement is to add a preservative (benzyl alcohol) for a multidose presentation in a 20 mL vial.

II. EFFECTIVENESS:

To address unknown characteristics associated with the addition of 2% benzyl alcohol preservative to PROPOFLO's approved formulation (NADA 141-098), a new field safety study was conducted.

A. Dosage Characterization:

This supplemental approval does not significantly change the previously approved dosage range. The Freedom of Information (FOI) Summary for the original approval of NADA 141-098 dated March 13, 1998, contains dosage characterization information for dogs.

B. Substantial Evidence:

This supplemental approval does not significantly impact the previously approved effectiveness information. The FOI Summary for the original approval of NADA 141-098 dated March 13, 1998, contains a summary of studies that demonstrate effectiveness of the unpreserved anesthetic drug for dogs.

For the approval of the multidose preserved propofol product, a single clinical field study evaluated safety and effectiveness and confirmed appropriate doses.

1. Clinical Field Study

(a) Study Title and Number: Evaluation of multidose propofol for the induction and maintenance of anesthesia in dogs. Study Number 05-02-MC-D-CT-H.

(b) Type of Study: Field effectiveness and safety study

(c) Study Investigators:

Table 1: Clinical Field Study Investigators and Locations

Name	City	State
James S. Gaynor, DVM, MS, DACVA	Colorado Springs	Colorado
Ralph C. Harvey, DVM, MS, DACVA	Knoxville	Tennessee
Khursheed Mama, DVM, DACVA	Fort Collins	Colorado
Sheilah Robertson, BVMS (Hons), PhD, DACVA, DECVA, MRCVS	Gainesville	Florida
Edwin A. Howe, DVM	Ocala	Florida
Alan J. Krause, DVM	Ocala	Florida

(d) General Design:

1. Study Objectives: The objectives of the clinical investigation were to determine the effective dose of PROPOFLO 28, with and without preanesthetics, and evaluate its safety as an intravenous anesthetic agent in client-owned dogs when

used for a) induction of anesthesia, b) maintenance of general anesthesia for up to 20 minutes or c) induction of general anesthesia where maintenance is provided by inhalant anesthetics.

- Description of Control and Treatment Groups: Each animal served as its own control. Treatment groups were selected to reflect routine veterinary clinical practice and included those preanesthetics and inhalant anesthetics most often used by veterinarians in private practice. Animals were assigned to anesthetic protocol (treatment group) according to patient needs. Groups 1-3 included only patients requiring general anesthesia for anticipated short procedures of <20 minutes (for example, physical exams, radiography, biopsy, endoscopy, minor surgery, etc.). Groups 4-6 included patients requiring procedures generally longer than 20 minutes and the use of an inhalant for maintenance of anesthesia. The table summarizes the description of the treatment groups.

Table 2: Clinical Field Study Treatment Groups

Group	Induction Agent	Premedicant Sedative	Maintenance Agent	n
1	PROPOFLO 28	None	PROPOFLO 28 (if needed)	23
2	PROPOFLO 28	Midazolam/Buprenorphine	PROPOFLO 28	25
3	PROPOFLO 28	Acepromazine/Buprenorphine	PROPOFLO 28	25
4	PROPOFLO 28	Midazolam/Buprenorphine	Inhalant	22
5	PROPOFLO 28	Acepromazine/Buprenorphine	Inhalant	22
6	PROPOFLO 28	Medetomidine/Buprenorphine	Inhalant	21

- Description of Test Animals: A total of 138 dogs of ASA status I or II requiring general anesthesia for surgical or nonsurgical procedures were enrolled. Patients that were pregnant or had received an investigational drug within 30 days were excluded. No limitation was placed on breed, age or gender of the patient.

Number: 138

Breed: Forty four (44) breeds were represented in the investigation. Other than dogs of mixed ancestry (n=34), Labrador Retrievers (n=13) and Yorkshire Terriers (n=7) were most frequently represented.

Age: Dogs enrolled in this investigation ranged in age from 3 months to 17 years and weighed from 1.8 to 51.5 kg. Mean age varied from a low of 3 years in Group 5, to a high of 8 years in Group 2.

Weight: Mean group weights and distribution were similar among all treatments and ranged from a low of 14 kg in Group 4 to a high of 21.6 kg in Group 2.

Sex: 78 males and 60 females

Health Status: ASA classification breakdown was: ASA I, n=101; ASA II, n=37.

4. **Statistical Analysis:** Descriptive statistics were obtained on the data; treatment groups could not be compared statistically in an unbiased manner because animals were not randomly assigned to treatment groups.

5. **Materials and Methods:**

Surgical Procedures:

The individual or combination medical/surgical procedures performed on the 138 dogs enrolled in this investigation are grouped into the following major categories: surgical/invasive, n=43; non-surgical/minimally invasive, n=76; and diagnostic/non-invasive, n=23. The most prevalent procedures were castration/neutering (n=35), dental (n=33), mass removal (n=19), radiographs (n=13) and ovariectomy (n=10). The diagnostic/non-invasive procedures were more heavily represented in Groups 1 and 2. Non-surgical/minimally invasive procedures predominated in Groups 3 through 6. Surgical/invasive procedures tended to be most heavily represented in Groups 4 through 6.

Anesthetic Procedures:

PROPOFLO 28 administration: The induction dose of PROPOFLO 28 was given to effect to produce a level of anesthesia sufficient for endotracheal intubation as judged by muscle relaxation, level of consciousness, and jaw tone of the patient. An injection time of 60-90 seconds was recommended in the protocol. If the first attempt at intubation failed due to inadequate muscle relaxation or unconsciousness, additional propofol was given. Dogs assigned to Groups 1 through 3 breathed either room air or supplemental oxygen after induction. In most cases, animals in these groups required maintenance doses of PROPOFLO 28 to complete the anesthetic procedure.

Premedicants:

Atropine was optional for all treatment groups. Administration of preanesthetics was performed according to the clinical practice standards of each test facility. Dose ranges and routes of premedicants are provided in Table 3.

Table 3: Premedicants used in Clinical Field Study

Premedicant	n	Dose, mg/kg		Route(s)
		Mean	Range	
Midazolam	47	0.259	0.020 - 0.475	SQ, IM, IV
Acepromazine	47	0.136	0.010 - 1.493	SQ, IM
Medetomidine	21	0.014	0.004 - 0.028	SQ, IM
Buprenorphine	115	0.014	0.0004 - 0.102	SQ, IM
Atropine	38	0.034	0.020 - 0.075	SQ, IM

Gas anesthetic:

Dogs assigned to Groups 3 through 7 were connected to the appropriate vaporized inhalant anesthetic immediately after intubation. A precision out-of-circle vaporizer and an in-circle CO₂ absorbent were used in the rebreathing systems. In general, the animals were allowed to breathe spontaneously during the procedure and, if hypoventilation occurred, controlled or assisted ventilation was provided and recorded.

Variables Measured or Observed:

Anesthetic Dose: The amount and time of each dose of propofol was recorded as well as the time of injection. In Groups 4 through 6, vaporizer concentrations and flow rates were also recorded at each change.

Anesthetic Response: The investigator assigned a subjective evaluation to the induction, maintenance and recovery from anesthesia as Excellent, Good, Fair or Poor. Recovery times were recorded.

Physiological: Heart rate (HR), arterial blood pressure (BP), respiratory rate (RR), body temperature, end-tidal CO₂ and percent oxygen (hemoglobin) saturation were recorded at specified times before and during the procedure. The investigator recorded all adverse reactions observed throughout the study for specified time intervals. Particular attention was paid to, but not limited to, cardiorespiratory, musculoskeletal, gastrointestinal, central nervous system, ocular and behavioral phenomena. The frequency and duration of apnea was documented.

(e) Results

1. Anesthetic Dose:

Induction:

Since the induction protocol was identical for Groups 2 and 4, and for Groups 3 and 5, a combined mean induction dose was computed for each group and presented in Table 4. Each of the premedicant combinations markedly reduced the PROPOFLO 28 induction dose requirements.

Table 4: Induction Dose by Preanesthetic Group

Groups	Preanesthetic(s)	n	Mean Total Dose (mg/kg)	Range (mg/kg)
1	None	23	7.6	4.62 - 16.0
2 and 4	Midazolam/Buprenorphine	47	4.7	2.19 - 8.33
3 and 5	Acepromazine/Buprenorphine	45	4.0	1.76 - 5.10
6	Medetomidine/Buprenorphine	20	3.2	1.71 - 7.50

The mean injection duration and injection rates (mg/kg/min) for combined treatment groups are provided in Table 5.

Table 5: Mean Injection Duration and Rate by Preanesthetic Group

Group	Preanesthetic	Mean Injection Duration (min)			Mean Injection Rate (mg/kg/min)		
		n	Mean	Range	n	Mean	Range
1	None	23	1.59	1.00 - 3.48	25	5.24	2.31 - 8.00
2 and 4	Midazolam/Buprenorphine	44	1.33	0.75 - 2.37	50	3.23	1.02 - 7.04
3 and 5	Acepromazine/Buprenorphine	45	1.21	0.50 - 2.42	40	3.53	1.87 - 5.32
6	Medetomidine/Buprenorphine	20	1.16	0.75 - 2.03	20	2.85	0.86 - 7.50

A lower induction dose of propofol appears to be needed in older dogs (see Table 6) maintained under anesthesia with PROPOFLO 28.

Table 6: Impact of Patient Age on Mean Induction Dose in Groups 1-3

Age, yr	0-1	>1-5	>5-9	>9
Induction Dose, mg/kg	6.34	5.68	5.48	4.86

The duration of anesthesia following induction with propofol is measured from the start of the induction dose to the first maintenance dose of propofol (Groups 1 through 3), as shown in Table 7.

Table 7: Duration of Anesthesia Following Induction in Groups 1-3

Group	N	Duration of anesthesia following induction, min	
		Mean	Range
1	15	5.79	1.32 - 11.2
2	18	5.47	1.00 - 20
3	19	6.49	0.17 - 16

Maintenance with PROPOFLO 28:

The number of PROPOFLO 28 doses administered during maintenance ranged from 0-11 and the total maintenance time was 5.32, 14 and 10.3 minutes in Groups 1, 2 and 3, respectively. The mean duration of procedures in Groups 1, 2, and 3 was 14.6, 19.7, and 18 minutes, respectively. The average maintenance doses (mg/kg) were 3.22 (range 1.1-6.78) for Group 1, 1.67 (range 0.88-6.35) for Group 2, and 2.03 (range 0.78-5.33) for Group 3, representing a sparing of 48% with midazolam and buprenorphine and 37% sparing with acepromazine and buprenorphine.

Maintenance with Inhalants:

Of the 65 animals maintained on inhalant, 56 were maintained with isoflurane and 9 with sevoflurane. The mean duration of anesthesia in Groups 4, 5, and 6, was 54.9, 96.9 and 46.4 minutes, respectively. Additional dose(s) of PROPOFLO 28 were administered to deepen anesthesia in 9 cases in Groups 4-6, respectively. Apnea occurred in a single case in conjunction with the administration of a supplemental dose of PROPOFLO 28.

2. Anesthesia Induction Quality:

The quality of induction was judged by the investigator. The quality of induction was judged as excellent in 82 (59%) of 138 total cases. It was rated as good in 47 (34%) of the cases, fair in 8 (6%) of the cases and poor in 1 (1%) of the cases. Five of the 9 inductions judged fair or poor involved those cases in which additional doses of propofol were required.

3. Maintenance Anesthesia Quality

Maintenance With PROPOFLO 28:

Investigator evaluation of the quality of maintenance of anesthesia varied between the three groups where propofol was used to maintain anesthesia. The percentage of cases rated good or excellent was 100% (19/19 cases) and 91% (23/24 cases rated) in Groups 1 and 3 respectively. However, the combined percentage rated good or excellent in Group 2 was 68% (17/25 cases). The percentage rated fair in Group 2 was 24% (6/25 cases), and 2 animals were rated as poor (8%). One animal in Group 3 was rated as fair (4%). In all, 9 animals maintained on propofol had a maintenance quality rated as fair or poor. Note that percentages in Group 3 will not add to 100% due to a missing quality rating in this group.

Maintenance with Inhalants:

Investigator evaluation of the quality of maintenance by inhalants following propofol induction varied among the groups. The maintenance quality of inhalants after PROPOFLO 28 induction was rated good to excellent in 96% of those animals in Group 4 (21/22 cases), 91% in Group 5 (20/22 cases), and 95% in Group 6 (20/21 cases). In all, only 4 animals undergoing inhalant maintenance had a reported maintenance quality of fair. No animal maintained on inhalant had a maintenance quality score of poor.

4. Supplemental Oxygen during Maintenance:
 Oxygen supplementation was optional for those groups maintained with propofol, however more than half of the animals in groups 1-3 (52% in Group 1, and 60% in each of Groups 2 and 3) received supplemental oxygen during the procedures.
5. Recovery Times Following Maintenance with PROPOFLO 28:

Table 8: Mean Recovery Times for Dogs Maintained with PROPOFLO 28

Group		Mean Time to Swallow (min)	Mean Time to Extubation (min)	Mean Time to Sternal Recumbency (min)	Mean Time to Standing (min)
1	Mean	9.11	9.71	11.3	16.2
	Range	2 – 41	2 – 41	3 – 44	7.92 – 56
	N	23	22	23	23
2	Mean	12.4	13.2	17.5	26.9
	Range	4 – 39	5 – 41	6 – 45	9.67 – 48
	N	23	25	25	25
3	Mean	11	11.5	15	21.1
	Range	3 – 23.5	3.83 – 24.5	4.83 – 28.5	6.83 – 48
	N	25	25	25	25

The mean times to sternal recumbency measured from extubation, were on average 1.9 minutes in Group 1, 4.53 minutes in Group 2 and 3.8 minutes in Group 3. The mean times from extubation to standing recovery were 6.41 minutes in Group 1, 13.7 minutes in Group 2 and 9.59 minutes in Group 3. Group 2 exhibited longer recovery times in general. It should be noted that, in this study, the standard deviations for all recovery parameters are large (in some cases larger than the mean values themselves), indicating that any differences seen between groups are likely not significant.

Recovery Times Following Maintenance with Inhalants:

Mean times to the return of swallowing were 7.86 minutes for Group 4, 9.4 minutes for Group 5, and 7.75 minutes for Group 6. The mean times to extubation, and then to sternal recumbency were similar to those seen in propofol maintenance groups. Mean times to extubation were 8.9 minutes in Group 4, 11 minutes in Group 5 and 9.19 minutes in Group 6. The mean times to sternal recumbency as measured from extubation were also similar to those in groups maintained with propofol: 2.23 minutes in Group 4, 4.32 minutes in Group 5, and 3.15 minutes in Group 6. The mean times from extubation to standing recovery, however, were longer than seen in groups maintained with propofol: 9.99 minutes in Group 4, 19.3 minutes in Group 5, and 13.6 minutes in Group 6.

Generally, the recovery times were shorter in the absence of carprofen, however this likely reflected the longer duration of anesthesia which was observed in animals subsequently dosed with carprofen.

6. Anesthesia Recovery Quality

Maintenance With PROPOFLO 28:

Investigators evaluated the quality of recovery as good to excellent in 91% (21/23) of non-premedicated animals (Group 1) and 88% (22/24) in animals receiving acepromazine and buprenorphine as a preanesthetic combination (Group 3). In those animals receiving midazolam and buprenorphine as a preanesthetic combination, however, the percentage rated good to excellent was lower, 76% (19/25) in Group 2 (see Table 9 below). In the balance of the animals maintained with PROPOFLO 28, the quality of recovery from anesthesia was rated fair. There were no ratings of poor following PROPOFLO 28 maintenance.

Maintenance With Inhalants:

The quality of recovery for all groups is shown in the following table. Recovery was rated good to excellent in 82% (18/22) of animals in Group 4, 81% (17/21) in Group 5 and 81% (17/21) in Group 6. Two animals receiving inhalants received poor recovery quality ratings. Seven animals receiving inhalant maintenance had recoveries that were rated fair.

Table 9: Quality of Recovery after Anesthesia

Group	Quality of Recovery					Total
	Excellent	Good	Fair	Poor	NA ^a	
	N (%)	N (%)	N (%)	N (%)	N (%)	
1	10 (43)	11 (48)	2 (9)	0	0	23
2	8 (32)	11 (44)	6 (24)	0	0	25
3	10 (40)	12 (48)	2 (8)	0	1 (4)	25
4	7 (32)	11 (50)	3 (14)	1 (5)	0	22
5	15 (68)	5 (23)	1 (5)	0	1 (5)	22
6	15 (71)	2 (10)	3 (14)	1 (5)	0	21
Total	65 (47)	52 (38)	17 (12)	2 (1)	2 (1)	138

^aNA = not applicable; one observation was missing in each of Groups 3 and 5.

7. Physiological Effects:

Mean values for heart rate (pulse), respiration rate, and mean arterial blood pressure are provided in the following table, measured prior to preanesthesia, prior to induction, and 5 minutes after induction. PROPOFLO 28 had a minimal effect on pulse, and a depressant effect on blood pressure and respiration rate.

Table 10: Pulse, Respiratory Rate and Blood Pressure

Group	Mean Pulse, bpm			Mean Respiratory Rate, breaths/min			Mean Blood Pressure, mm Hg		
	Before premed	Before induct.	5 min after induct.	Before premed	Before induct.	5 min after induct.	Before premed	Before induct.	5 min after induct.
1	NA	117.2	123.7	NA	41.6	31.2	NA	114.7	101.9
2	113.0	112.8	110.0	41.1	36.4	27.1	108.9	102.3	85.8
3	107.6	96.9	101.0	30.6	30.3	24.6	107.8	96.2	83.7
4	127.8	135.9	146.8	34.8	34.4	25.7	103.7	109.8	78.0
5	116.8	145.1	158.1	28.6	29.9	17.4	113.1	105.6	79.7
6	115.6	88.4	104.1	42.4	30.7	13.8	115.1	107.1	92.6

8. Adverse Reactions:

Table 11 summarizes all abnormal clinical observations reported, by body system, in descending order of frequency of individual occurrence.

Table 11: Field Study Adverse Reactions

Observation	System	No. of Dogs
Hypotension	Cardiovascular	16
Apnea	Respiratory	15
Excitation	Central Nervous System	13
Bradycardia	Cardiovascular	11
Tachypnea	Respiratory	7
Fasciculation	Muscular	4
Paddling	Muscular	4
Hypertension	Cardiovascular	3
Tenseness	Muscular	3
IPPV*	Respiratory	3
Arrhythmias	Cardiovascular	2
Cyanosis	Cardiovascular	2
Salivation	Gastrointestinal	2
Tachycardia	Cardiovascular	2
Emesis	Gastrointestinal	1

*Intermittent Positive Pressure Ventilation

The adverse reactions observed in this study were similar to those identified previously for propofol.

The following specific adverse reactions were particularly noted during the study: apnea of duration greater than 120 seconds, a heart rate of less than 50 beats per minute, a mean indirect arterial blood pressure of less than 50 mmHg, any potentially lethal ECG rhythm, and mean oxygen saturation of less than 80% (for any duration) or less than 90% for more than 3 minutes.

Apnea, bradycardia, and hypotension, were commonly reported adverse reactions. Cyanosis, emesis and heart block also occurred. Apnea occurred mainly in Groups 1 through 3 (9 occurrences vs. 3 in Groups 4 through 6). Hypotension, by contrast, was more often associated with the use of inhalants. In all, 20 adverse reactions were rated mild in severity, and 11 were considered moderate in severity by the attending investigators.

One dog died during the study. A 6-year-old female Jack Russell Terrier from Group 5, was found dead in its kennel 3 days following an ovariohysterectomy. A necropsy was performed and the cause of death was found to be sepsis from a post-operative infection, likely the result of incidental debris in the surgical wound. Three other dogs were anesthetized from the same vial without incident. Following post-mortem examination, the investigator stated that the adverse reaction was unrelated to the use of PROPOFLO 28.

(f) Conclusions

This field study, evaluating PROPOFLO 28, a preparation of propofol containing up to 2% benzyl alcohol as a preservative, for induction and maintenance of anesthesia in dogs, supports the following conclusions:

1. The addition of the benzyl alcohol preservative allowed the use of one propofol vial for up to 9 needle insertions for drug withdrawal over a period up to 17 days.
2. The addition of benzyl alcohol did not significantly affect the induction dose, the time between injection of propofol and intubation, or the mean dose necessary to maintain anesthesia.
4. The quality of induction, maintenance, and recovery seen with the use of PROPOFLO 28 was comparable to that seen without benzyl alcohol preservative.
5. The main adverse reactions of apnea, bradycardia and hypotension were comparable to those observed with other propofol formulations.
6. The number and severity of adverse reactions were not increased by the addition of benzyl alcohol to the propofol preparation.

III. TARGET ANIMAL SAFETY:

A. Type of Study: Tolerance

1. Title: PROPOFLO 28 (multidose): A tolerance study following intravenous dose administration in Beagle dogs; Study Number 04-03-IT-D-TL-H.
2. Study Director: Josee J. Laliberté, PhD, ITR Laboratories Canada, Inc., Montreal, Canada

3. Study Design:

- a. Objective: This study was conducted to evaluate the tolerance of young adult, unpreanesthetized Beagle dogs to various doses of the investigational drug product, PROPOFLO 28, in comparison to unpreserved PROPOFLO. This study was conducted in accordance with Good Laboratory Practice Regulations (GLPs; 21 CFR 58).
- b. Study Animals: Two female and 2 male Beagle dogs, young adults (5 – 6 months), 6.2 – 8.3 kg.
- c. Treatment Groups: Each dog received all treatments with at least a 7 day washout period between treatments.

Table 12: Treatment Groups

Treatment No.	Study Day	Treatment	Propofol (mg/kg)	Benzyl Alcohol (mg/kg)
1 (0X)	1	Saline ¹	0	0
2 (3X)	10	PROPOFLO ²	19.5	0
3 (1X)	20	PROPOFLO 28 ³	6.5	13
4 (3X)	27	PROPOFLO 28	19.5	39
5 (3X)	50	PROPOFLO ²	19.5	0

- 1. A volume of saline equal to the volume of 19.5 mg/kg PROPOFLO and PROPOFLO 28.
- 2. Active Control at the high dose (3X).
- 3. Additional administrations of PROPOFLO 28 were required for two animals to achieve intubation: 3.2 mL (a total of 11.6 mg/kg) for animal no. 1510A and 0.86 mL (a total of 7.5 mg/kg) for animal no. 1001A.

- d. Drug Administration: Each dose was administered at a rate of 2 mL over approximately 10 seconds as a single intravenous bolus injection. PROPOFLO 28 was the investigational drug product, the negative control was 0.9% Sodium Chloride for Injection, and the active control was 10 mg/mL PROPOFLO injectable emulsion.
- e. Measurements and Observations:

Table 13: Study Variables

Mortality	Once daily
Cage-side clinical signs (ill health, behavioral changes, etc.)	Once daily on non-treatment days, and twice daily on treatment days
Observations during treatment or anesthesia	Recorded as they occurred
Body weights	Study days 1, 3, 10, 12, 20, 22, 27 29, 50
Duration of anesthesia	End of injection to return of the swallow reflex
Recovery from anesthesia	Time of the swallow reflex to sternal recumbency
Diastolic, systolic, and mean blood pressures using an indirect measurement	Immediately after intubation and then every 5 minutes from the time of injection up to the reversal of anesthesia (reestablishment of swallowing reflex) or 30 minutes post-dosing in the negative control group
Heart rate and electrocardiograms (leads I, II, III, aVR, aVL, aVF); assessed by a consultant cardiologist	
Arterial blood oxygen saturation (SpO ₂) using an oximeter (not measured in negative control group)	
End tidal CO ₂ obtained using a capnograph (not measured in negative control group)	
Respiratory rate by observation	
Body temperature (rectal)	
Mucous membrane color: normal (pink), white (pale) or grey/blue (purple/blue)	
Hematology: Blood samples were collected in a fasted state, once prior to each treatment and then 2 days following each treatment. Hematology was not performed for the second high dose of PROPOFLO.	

<p>Chemistry: Blood samples were collected in a fasted state, once prior to each treatment and then 2 days following each treatment. Chemistries were not performed for the second high dose of PROPOFLO.</p>	<p>Calculated A/G ratio, alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, total bilirubin, calcium, chloride, total cholesterol, creatinine, calculated globulin, glucose, inorganic phosphorus, potassium, sodium, total protein, triglycerides, urea</p>
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f. Statistical analysis: Descriptive statistics were calculated and summarized by treatment group for the continuous variables measured in the study.

4. Results:

- a. Cage-Side Clinical Observations: Observations included vomiting and diarrhea, and did not appear to be associated with treatments.
- b. Observations During Anesthetic Periods: There were no abnormal findings during treatments with saline, the first high dose of PROPOFLO, and the low dose of PROPOFLO 28. All abnormal observations noted after treatment occurred with the high dose of PROPOFLO 28 and second high dose of PROPOFLO during recovery. Apnea was not recorded.
- c. Duration of Anesthesia and Recovery Period: There was a dose dependent effect on anesthetic and recovery times between the low and high doses of PROPOFLO 28. There was no trend between individual recovery times during treatments.

Table 14: Mean Anesthetic and Recovery Time (minutes)

Treatment	Duration of Anesthesia	Duration of Recovery
High Dose PROPOFLO (1)	13.68 SD = 3.937	5.23 SD = 4.276
Low Dose PROPOFLO 28	6.74 SD = 2.354	4.50 SD = 2.083
High Dose PROPOFLO 28	15.53 SD = 5.609	10.93 SD = 5.134
High Dose PROPOFLO (2)	15.26 SD = 5.234	9.04 SD = 8.668

d. Tachycardia occurred in all dogs immediately post intubation for all treatments, and was most pronounced during treatment with the high dose of

PROPOFLO 28 compared to PROPOFLO at the same dose. Mean heart rates during all treatments tended to decrease with time.

Table 15: Mean Heart Rates

Tx	Post Intubation	Time in Minutes Post Intubation					
		5	10	15	20	25	30
1	145*	130	150	130	123	138	140
2	193	168	147 n=3	145 n=2			
3	183	168	130 n=1				
4	218	178	128	115 n=2	100 n=1		
5	195	153	127 n=3	107 n=3	110 n=1		

* Dogs in the saline control group were not intubated; times are post-dose.

- e. Electrocardiograms: All post-intubation ECGs had variable degrees of sinus tachycardia with both PROPOFLO and PROPOFLO 28. Treatment with PROPOFLO 28 had a dose-dependent effect on sinus tachycardia, and induced a higher degree of sinus tachycardia compared to PROPOFLO at the same dose. During all treatments, the cardiologist did not note any clinically significant effects on the morphology of the P-QRS-T complexes.
- f. Body Temperature: Mean body temperatures remained relatively normal at 0, 5, 10, 15, 20, 25, and 30 minutes post-intubation for all dogs during treatments 1, 2, and 3. Mean body temperatures decreased the most during treatment with the high dose of PROPOFLO 28 compared to all other treatments, falling from 101.5 °F to 99.7 °F (n=1) at 20 minutes post intubation
- g. Mucous Membrane Color: Except for one dog which exhibited gray/blue mucous membranes following treatments 2 and 4, mucous membrane color remained normal during all treatments.
- h. Respiratory Rates (bpm): Mean respiratory rates never fell to an unacceptable level. The most pronounced decrease in mean respiratory rates occurred during treatment with the high dose of PROPOFLO 28, at 5 minutes post intubation.

Table 16: Mean Respiratory Rates

Tx	Post Intubation	Time Post Intubation (min)					
		5	10	15	20	25	30
1	34*	33	28	29	27	30	29
2	22	23	20 n=3	16 n=2			
3	24	24	24 n=1				
4	22	16	20	16 n=2	20 n=1		
5	18	18	15 n=3	14 n=2	12 n=1		

* Dogs in the saline control group were not intubated; times are post-dose

- i. End Tidal Carbon Dioxide (ETCO₂): All mean ETCO₂ values were greater than high normal (40 mm Hg) at 5 minutes post intubation.

Table 17: Mean ETCO₂

Tx	Post Intubation	Time Post Intubation (minutes)					
		5	10	15	20	25	30
1	N/A						
2	36	46	42	36.5 n=2			
3	32	48	40 n=1				
4	41	47	42	34 n=3	38.5 n=2	30 n=1	
5	39	48	38 n=3	36 n=3	41 n=1		

- j. Arterial Blood Oxygen Saturation (SpO₂): Except during treatment with the low dose of PROPOFLO 28, SpO₂ increased at 5 minutes post intubation.

Table 18: Mean O₂ Saturation

Tx	Post Intubation	Time in Minutes Post Intubation					
		5	10	15	20	25	30
1	N/A						
2	64	81	92	88 n=2			
3	82	76	90 n=1				
4	57	78	91	93 n=3	92 n=2	92 n=1	
5	64	79	91 n=3	91 n=3	90 n=1		

- k. Systolic, Diastolic, and Mean Arterial Pressures: Mean systolic pressures remained in the normal range after 5 minutes post intubation. Immediately post intubation all systolic pressures were high. Mean diastolic pressures decreased to normal 5 minutes post intubation after all treatments except during the saline control, and treatment with the low dose of PROPOFLO 28.

Table 19: MAPs (mm Hg)

Tx	Post Intubation	Time in Minutes Post Intubation					
		5	10	15	20	25	30
1	124	122	123	141	128	135	119
2	134	113	109 n=3	122 n=4			
3	133	121	120 n=1				
4	131	109	103	109 n=2	94 n=1		
5	136	105	98 n=3	103 n=3	107 n=1		

- l. Body Weights: Body weights remained stable throughout the study.
- m. Clinical Pathology: Hematology and chemistries were not analyzed pre and post treatment with the second high dose of PROPOFLO. There were mild changes in hematology, most within normal ranges. There was a mildly increased mean MCHC pre and post treatment with saline and the low dose of PROPOFLO 28, and mildly increased mean MCHC post treatment with the high dose of PROPOFLO and the high dose of PROPOFLO 28. There were mild changes in the chemistry values, all within normal ranges.
- n. Urinalysis: Not performed.

Conclusions: This study demonstrated that the addition of 2% benzyl alcohol to PROPOFLO at an induction dose of 6.5 mg/kg and an exaggerated dose of 19.5 mg/kg in 4 Beagle dogs did not produce unexpected serious adverse reactions. Clinically significant effects of the PROPOFLO and PROPOFLO 28 on variables in this study include sinus tachycardia, decreases in body temperature and blood pressure, abnormal mucous membrane color, tachypnea, increased end tidal CO₂, decreased SpO₂, and transient hypertension.

IV. HUMAN FOOD SAFETY:

This drug is intended for use in dogs, which are non-food animals. 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 NADA.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to PROPOFLO 28:

Not for human use. Keep out of the reach of children.
Rare cases of self-administration have been reported, including fatalities. Propoflo 28 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. The Material Safety Data Sheet (MSDS) contains more detailed occupational safety information. For customer service, adverse effects reporting, and/or a copy of the MSDS, call (888) 299-7416.

VI. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 514. The data demonstrate that PROPOFLO 28, when used according to the label, is safe and effective for the induction and maintenance of general anesthesia.

A. Marketing Status:

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional veterinary expertise is required to administer general anesthesia to dogs.

B. Exclusivity:

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval. The three years of marketing exclusivity applies only to the PROPOFLO 28 multidose formulation for which this supplement is approved.

C. Supplemental Applications:

This supplemental NADA did not require a reevaluation of the safety and effectiveness data in the original NADA (21 CFR 514.106(b)(1)).

D. Patent Information:

PROPOFLO 28 is under the following U.S. patent numbers:

<u>U.S. Patent Number</u>	<u>Date of Expiration</u>
6,140,373	10/23/2018

For current information on patents, see the Animal Drugs @ FDA database (formerly the Green Book) on the FDA CVM internet website.

VII. ATTACHMENTS:

Facsimile Labeling:

Package Insert

20 mL Vial Labeling

20 mL Carton