Date of Approval: May 21, 2010

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-303

PROPOCLEAR

propofol
Injectable
Cats and Dogs

For the induction and maintenance of anesthesia and for induction followed by maintenance with an inhalant anesthesic, in cats and dogs.

Sponsored by:

Fort Dodge Animal Health, Division of Wyeth,
a wholly owned subsidiary of Pfizer, Inc.

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I. GENERAL INFORMATION:

A. File Number:	NADA 141-303
B. Sponsor:	Fort Dodge Animal Health, Division of Wyeth, a wholly owned subsidiary of Pfizer, Inc. 235 East 42d St. New York, NY 10017 Drug Labeler Code: 000856
C. Proprietary Name(s):	PROPOCLEAR
D. Established Name(s):	Propofol
E. Pharmacological Category:	Anesthestic
F. Dosage Form(s):	Microemulsion
G. Amount of Active Ingredient(s):	10 mg/mL
H. How Supplied:	20 mL sterile multi-dose vial 50 mL sterile multi-dose vial 100 mL sterile multi-dose vial
I. How Dispensed:	Rx
J. Dosage(s):	

Induction of General Anesthesia in Cats: Induction dose guidelines are 4.1 - 8.0 mg/kg for cats that do not receive a preanesthetic, and 2.7 - 8.0 mg/kg for cats that receive a preanesthetic. The PROPOCLEAR induction dose is reduced by 16-24% for cats that receive a preanesthetic (dose sparing effect). Anesthesia is usually observed within 60 seconds after the end of the induction dose administration. Duration of anesthesia following the recommended induction dose is approximately 3 minutes without a preanesthetic and 3-6 minutes with a preanesthetic. Full standing recovery occurs within approximately 30 minutes in cats. Individual anesthesia times vary. Induction doses for cats given PROPOCLEAR alone, or when PROPOCLEAR is preceded by a preanesthetic, are indicated in the following table. The table is for guidance only. The actual induction dose should be based on patient response.

PROPOCLEAR (10 mg/mL) Induction Dose Guidelines: Cats			
Preanesthetic	**Mean Induction Dose (mg/kg)**	**Induction Dose Range (mg/kg)**	**Induction Dose Sparing**
None	7.4	4.1 – 8.0	0%
Phenothiazine + Opioid	6.2	2.7 – 8.0	16%
Alpha$_2$-adrenoreceptor agonist	5.6	3.3 – 8.0	24%
Benzodiazepine + Opioid	6.2	3.1 – 8.0	16%

Maintenance of General Anesthesia in Cats: Anesthesia can be maintained by administration of PROPOCLEAR using intermittent IV injections. For cats, the duration of anesthesia following each PROPOCLEAR maintenance dose is approximately 3-5 minutes. Clinical response may vary, and is determined by the dose, rate of administration and frequency of maintenance injections. PROPOCLEAR maintenance dose sparing is greater in cats that receive a preanesthetic. The maintenance dose and frequency should be based on the patient's response. The following table is provided for guidance.

PROPOCLEAR (10 mg/mL) Maintenance Dose Guidelines: Cats		
Preanesthetic	**Mean Maintenance Dose (mg/kg)**	**Maintenance Dose Range (mg/kg)**
None	1.9	0.6 – 3.3
Phenothiazine + Opioid	2.3	0.8 – 5.0
Alpha$_2$-adrenoreceptor agonist	2.2	1.0 – 3.4
Benzodiazepine + Opioid	2.3	1.1 – 3.6

Inhalant Anesthetic Maintenance of General Anesthesia in Cats: Additional low doses of PROPOCLEAR, similar to a maintenance dose, may be necessary to facilitate the transition to inhalant maintenance anesthesia.

K. Route(s) of Administration: Intravenous injection

L. Species/Class(es): Cats

M. Indication(s): For the induction and maintenance of anesthesia and for induction followed by maintenance with an inhalant anesthetic, in cats and dogs.

II. EFFECTIVENESS:

A. Dosage Characterization:

Study Title and Number: Pharmacokinetics and pharmacodynamics of propofol administered to cats in a novel, aqueous, nano-droplet formulation or RAPINOVET emulsion formulation (Study No. 0989-F-US-01-05).

A single-dose comparative bioavailability study of PROPOCLEAR and RAPINOVET (NADA 141-070) characterized the effective dose in cats as 7.0 mg/kg. In a two-treatment, two-period crossover study, 10 adult, purpose-bred, domestic short hair female cats, aged approximately 22 to 33 months, with a mean weight of 3.78 kg, received 7.0 mg/kg of PROPOCLEAR or RAPINOVET as an intravenous injection over approximately 30 seconds. Refer to Table 1 below, for a summary of the results.

Table 1: Mean Pharmacokinetic Parameters for PROPOCLEAR and RAPINOVET

Test Article	**Peak plasma concentration (C_{max}) (± 1SD)**	**Time of peak concentration (Tmax)**	**$AUC_{0-\infty}$ (± 1SD)**	**Half-life (± 1SD)**
PROPOCLEAR	5371 (1228) ng/mL	4 minutes	6306 (1173) hours·ng/mL	7.3 (1.6) hours
RAPINOVET	7062 (2322) ng/mL	6 minutes	6962 (1251) hours·ng/mL	8.8 (1.6) hours

The estimated ratio for mean C_{max} values (based on log-transformed data) of PROPOCLEAR relative to RAPINOVET is 0.78, and the 90% Confidence Interval Limits about the ratio is 0.59 to 1.03. Similarly, for comparison of mean $AUC_{0-\infty}$ values, the estimated ratio is 0.92 and the 90% Confidence Interval Limits about the ratio is 0.80 to 1.07. The mean $AUC_{0-\infty}$ values for the test articles are deemed equivalent. However, the mean C_{max} values for the test articles are not equivalent, because the 90% Confidence Interval does not meet the criterion: 0.80 to 1.25.

The pharmacodynamics of PROPOCLEAR and RAPINOVET were assessed by Investigator observation of key anesthetic events and physiologic parameters. There was no difference between test articles for observation of key anesthetic events that may be related to C_{max} values, such as time to lateral recumbency or time to onset of anesthesia. In addition, there was no indication of a difference between test articles for physiologic parameters (ECG, heart rate, blood pressure [systolic, diastolic and mean arterial], body temperature, respiration rate, and SpO_2).

Conclusion: The dosage characterization is acceptable for evaluation of product effectiveness.

B. Substantial Evidence:

Cat Field Study

Study Title and Number: Multicentric Field Study to Investigate the Efficacy and Safety of 1% w/v Propofol Injection in Cat Anesthesia (Study No. 0989-F-US-05-06).

Type of Study: Good Clinical Practices (GCP) field study.

Study Dates: February 2007 to June 2007

Investigators and Locations:

Investigators	Location
Scott Krick, DVM Ann Bastian, VMD Debbie Wardius, VMD	Sinking Springs, Pennsylvania
Phillip Lerche, B.V.Sc., MS, Ph.D. William Muir, DVM, Ph.D.	Columbus, Ohio
Kristi Lively, DVM Adele Mays, DVM	Knoxville, Tennessee
Roger Sifferman, DVM Bert Shelley, DVM	Springfield, Missouri
Samuel Geller, VMD	Quakertown, Pennsylvania

General Design:

1. Purpose: To determine the effectiveness and safety of propofol when administered to cats requiring anesthesia for short procedures, diagnostic tests, surgical and dental procedures. Effectiveness and safety were determined using phenothiazines, opioids, benzodiazepines, or alpha$_2$-adrenoreceptor agonists as preanesthetics, prior to induction with propofol, followed by maintenance anesthesia with propofol or isoflurane.

2. Description of Test Animals: One hundred sixty cats were enrolled in the study. Cat breeds included domestic short hair (122 cats), domestic long hair (18 cats), domestic medium hair (7 cats), Siamese (7 cats), Persians (2 cats), Himalayan (1 cat), Oriental Short Hair (1 cat), Abyssinian (1 cat), and Maine Coon (1 cat). The ages ranged from 13 weeks to 14.7 years. Weights ranged from 1.8 kg (4.0 lbs) to 9.6 kg (21.1 lbs), with a mean weight of 4.12 kg (9.0 lbs).

Eighty-two percent of the enrolled cats were ASA class 1 (healthy), 18% were ASA class 2 (mild systemic disease). Three cats were excluded from the effectiveness data. One hundred sixty cats were included in the safety analysis.

3. Treatment Groups: Cats were assigned to 1 of 8 treatment groups based on their anesthetic requirement. All cats received propofol for anesthesia induction.

Table 2: Preanesthetic and Anesthetic Treatment Groups, Cat

Group	Preanesthetic	Maintenance
1	None	Propofol
2	None	Isoflurane
3	Acepromazine + Butorphanol	Propofol
4	Acepromazine + Butorphanol	Isoflurane
5	Medetomidine	Propofol
6	Medetomidine	Isoflurane
7	Midazolam + Butorphanol	Propofol
8	Midazolam + Butorphanol	Isoflurane

The following mean dosages of preanesthetics were administered prior to propofol administration. The preanesthetic dose may be lower than the label directions for use as a single medication (Plumb, 2008).

Table 3: Preanesthetic Doses Used in Cat Field Study

Preanesthetic	Dosages Used	Route of Administration
Acepromazine	0.025 – 0.10 mg/kg	IM
Medetomidine	10.0 mcg/kg	IM
Midazolam	0.2 mg/kg	IM
Butorphanol	0.2 - 0.4 mg/kg	IM

4. Dosage Form: 1% w/v propofol microemulsion, intravenous injectable (commercial formulation).

5. Administration: Propofol was administered through indwelling intravenous catheters over approximately 60 seconds. Propofol was administered once, to effect (until intubation), up to a maximum dose of 8.0 mg/kg. Additional doses of propofol were administered if clinically necessary to achieve intubation. Once intubated, anesthesia was maintained either with intravenous doses of propofol or the inhalant anesthetic isoflurane.

6. Variables Measured: The study included physical examinations, serum chemistry, hematology, body weights, and observations of animals for clinical

signs. For anesthetic episodes, the study recorded the preanesthetic and propofol doses and times of administration, time to onset of lateral recumbency, time to onset of anesthesia, duration of apnea, end of anesthesia (extubation), time to sternal recumbency, overall anesthetic score, and observations of adverse reactions. Physiological responses documented during anesthesia included indirect systolic blood pressure, heart rate, body temperature, electrocardiogram (ECG), respiration rate, and blood oxygenation level by pulse oximetry (SpO_2). Physiological variables were assessed at predetermined times relative to the start of propofol administration. A dose sparing ratio was calculated for each preanesthetic treatment group by dividing the mean dose (mg/kg) of each preanesthetic treatment group by the mean dose of the treatment group that did not receive a preanesthetic.

7. Statistical Methods: Physiological variables, anesthetic times, induction dose, maintenance doses, and anesthesia scores were summarized by treatment groups as mean, standard deviation, minimum and maximum.

8. Procedures: Female ovariohysterectomy or male neutering in 58.8% of cats (94/160, 37 females and 57 males), either alone (88 cats) or associated with other procedures (6 cats); Dental cleaning or other dental procedures in 31.3% of cats (50/160), either alone (41 cats), or associated with other procedures (9 cats); Declaw in 8.8% of cats (14/160), either alone (7 cats), or associated with other procedures (7 cats); Other type of surgery in 6.3% of cats (10/160), either alone (9 cats) or associated with dental procedure (1 cat), including abscess surgery, grooming, abdominal exploration, entropion repair, hernia repair, laser treatment, allergy tests, computed tomography, and rhinoscopy; and Radiography in 4.4% of cats (7/160), always associated with a dental procedure.

9. Clinical Pathology Findings: Cats enrolled in the study had blood and urine samples collected for hematology, serum chemistry, urinalysis, and coagulation times prior to enrollment in the study (baseline). Additional clinical pathology was performed after anesthesia if the cat had abnormalities at baseline.

10. Results:
    Induction of Anesthesia: Time from preanesthetic administration until the start of propofol induction averaged about 25 minutes (range from 18 minutes to 53 minutes). For cats that did not receive a preanesthetic (Groups 1 and 2), an average of 7.4 mg/kg propofol was required to induce anesthesia. All preanesthetic treatments caused propofol dose sparing effects compared to controls that did not receive a preanesthetic. Induction doses were reduced by 16% in cats that received acepromazine and butorphanol preanesthetic (Groups 3 and 4), 24% in cats that received medetomidine preanesthetic (Groups 5 and 6), and 16% in cats that received midazolam and butorphanol preanesthetic (Groups 7 and 8).

Table 4: Mean Dosing and Anesthesia Parameters for All Treatment Groups[a], Cats

Variable Measured	Treatment Group							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Number of cats	21	19	20	20	20	21	20	20
Propofol Induction Dose (mg/kg)[b]	7.2	7.5	6.5	5.9	5.7	5.5	6.2	6.1
Propofol Dosing Time[c]	1:15	1:21	1:07	0:55	0:52	1:13	0:51	0:50
Time to Onset of Anesthesia	1:56	3:07	1:52	1:44	1:58	1:59	1:30	1:40
Duration of Anesthesia[d]	19:21	45:47	24:20	51:34	21:00	44:56	28:55	47:48
Duration of Recumbency[e]	0:37:07	1:05:47	0:50:59	1:07:53	0:50:14	1:05:38	0:59:38	1:04:18
Time to Standing Recovery[f]	31:37	33:44	37:36	23:54	39:45	28:03	40:24	24:15
Dose Sparing Ratio	1.00		0.84		0.76		0.84	

[a] All times are reported in min:sec or hr:min:sec
[b] Three cats in Group 1 were excluded from computation of treatment means because of extravascular administration of induction doses of propofol or failure to intubate/extubate.
[c] Interval between propofol infusion start and end times
[d] Interval from intubation to extubation
[e] Interval from lateral recumbency during induction until sternal recumbency during recovery
[f] Interval from extubation to standing recovery

Maintenance of Anesthesia: Table 5 summarizes data from cats that received propofol maintenance anesthesia. The mean propofol maintenance dose was 2.16 mg/kg, and differences in propofol maintenance doses between preanesthetic groups were small. Depending on the preanesthetic given, an average of 1.0 to 2.6 propofol maintenance doses were administered. In cats that did not receive a preanesthetic, duration of anesthesia following the propofol induction dose was approximately 2.5 minutes. The average time interval between propofol maintenance doses was approximately 3 minutes for cats that did not receive a preanesthetic, and approximately 5.5 minutes for cats that received a preanesthetic.

Table 5: Summary of Effectiveness Data for Propofol Maintenance Anesthesia

Variable Measured	Treatment Group			
	1	3	5	7
Number of Cats	21	20	20	20
Mean propofol maintenance dose (mg/kg)	1.9	2.3	2.2	2.3
Mean number propofol maintenance doses	2.0	2.6	1.0	2.1
Mean duration of anesthesia by induction dose [a] (min:sec)	2:30	2:51	5:54	5:55
Mean time interval between maintenance doses (min:sec)	3:19	3:27	5:29	5:36

[a] Interval from intubation to first maintenance dose (or extubation for cats not requiring maintenance anesthesia)

The concentration of isoflurane (inhalant anesthetic) required to maintain anesthesia was slightly higher in cats that did not receive a preanesthetic (2.64%) compared to cats that received a preanesthetic (2.30% to 2.35%).

Anesthesia Scores: Table 6 summarizes investigator assessment scores for quality of induction, maintenance and recovery for each treatment group.

Table 6: Summary of Quality of Anesthesia Score Frequencies in Cats

Anesthesia Phase	Treatment Group							
	1	2	3	4	5	6	7	8
Induction								
Excellent (%)	81.0	63.2	85.0	95.0	90.0	90.0	80.0	100.0
Acceptable (%)	19.0	36.8	15.0	5.0	10.0	10.0	20.0	0.0
Unacceptable (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Maintenance								
Excellent (%)	95.2	89.5	95.0	95.0	100.0	95.0	100.0	100.0
Acceptable (%)	4.8	10.5	5.0	5.0	0.0	5.0	0.0	0.0
Unacceptable (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Recovery								
Excellent (%)	81.0	63.2	75.0	90.0	75.0	80.0	60.0	75.0
Acceptable (%)	9.5	36.8	20.0	10.0	25.0	20.0	40.0	20.0
Unacceptable (%)	9.5	0.0	5.0	0.0	0.0	0.0	0.0	5.0

Adverse Reactions: Tables 7a and 7b summarize adverse reactions that occurred during anesthesia. These tables display the number of cats in each treatment group with adverse reactions between baseline observations made before preanesthetic administration through standing recovery.

In Tables 7a and 7b, three cats in which anesthesia was subsequently maintained with propofol had abnormal ECG before propofol induction, and 4 had abnormal ECG after propofol induction. Among the population of cats in which anesthesia was maintained with isoflurane, 2 cats had abnormal ECG before propofol induction, and 7 had abnormal ECG after induction with propofol.

Apnea was observed following induction of anesthesia with propofol in 3 cats, and occurred between 2 and 5 minutes after the start of the induction propofol dose administration. Apnea did not occur in any cat during maintenance anesthesia with propofol. One cat that did not receive a preanesthetic and was maintained with propofol experienced bradypnea.

One cat experienced hypertension (Group 7).

Table 7a: Summary of Adverse Reactions for Cats in Groups 1 - 4

Adverse Reaction	Group 1		Group 2		Group 3		Group 4	
	Before Propofol	After Propofol	Before Propofol	After Propofol	Before Propofol	After Propofol	Before Propofol	After Propofol
Abnormal ECG	2	1	0	1	0	1	0	2
Apnea (> 60 sec)	0	0	0	1	0	0	0	1
Bradycardia (≤ 90 bpm)	0	0	0	0	0	0	0	2
Bradypnea (< 10 bpm)	0	1	0	0	0	0	0	0
Emesis	0	1	0	0	0	0	0	0
Hypertension	0	0	0	0	0	0	0	0
Hypotension (≤ 90 mm Hg)[a]	0	1	2	12	7	9	2	16
Hypoxia (SpO_2 < 85%)	0	3	0	0	1	1	2	0
Tachycardia (≥ 180 bpm)	0	0	0	0	0	0	0	0

[a] Systolic blood pressure

Table 7b: Summary of Adverse Reactions for Cats in Groups 5-8

Adverse Reaction	Group 5		Group 6		Group 7		Group 8	
	Before Propofol	After Propofol	Before Propofol	After Propofol	Before Propofol	After Propofol	Before Propofol	After Propofol
Abnormal ECG	1	2	2	3	0	0	0	1
Apnea (> 60 sec)	0	0	0	0	0	0	0	1
Bradycardia (≤ 90 bpm)	3	2	2	2	0	1	0	2
Bradypnea (< 10 bpm)	0	0	0	0	0	0	0	0
Emesis	1	0	1	1	0	0	0	0
Hypertension	0	0	0	0	0	1	0	0
Hypotension (≤ 90 mm Hg)[a]	2	1	2	14	4	5	4	16
Hypoxia (SpO_2 < 85%)	1	0	2	0	0	0	0	0
Tachycardia (≥ 180 bpm)	0	0	0	0	0	1	0	1

[a] Systolic blood pressure.

Hypotension was considered an adverse reaction if systolic blood pressure was ≤ 90 mm Hg. Thirteen cats (16.0%) maintained with propofol experienced hypotension prior to induction of anesthesia with propofol, and 16 cats (19.8%) experienced hypotension after induction of anesthesia with propofol. Ten cats (12.7%) that received isoflurane maintenance anesthesia experienced hypotension prior to induction of anesthesia with propofol, and 58 cats (73.4%) experienced hypotension after induction of anesthesia with propofol and maintenance with

isoflurane. Hypotension secondary to vasodilation is a known effect of isoflurane, and hypotension secondary to myocardial depression occurs in animals given propofol.

Hypoxia (defined as SpO2 <85%) occurred in 6 cats before induction of anesthesia with propofol, and in 4 cats after induction of anesthesia. Because SpO2 was measured using pulse oximetry, many of the observations of SpO2 below 85% prior to induction of anesthesia with propofol were likely due to the difficulty of measuring SpO2 in conscious animals.

Tachycardia (HR ≥ 180 bpm) occurred in 2 cats following propofol induction (midazolam and butorphanol preanesthetic); anesthesia was maintained with propofol in 1 cat and with isoflurane in the other cat. One cat had received atropine during maintenance anesthesia.

Table 8: Number of Adverse Reactions During Anesthesia in Cats

Preanesthetic	**Number of Adverse Reactions During Anesthesia[a]**		
	Propofol Maintenance	**Isoflurane Maintenance**	**Total**
No preanesthetic	8	18	26
Acepromazine + Butorphanol	13	28	41
Medetomidine	6	21	27
Midazolam + Butorphanol	10	25	35
All preanesthetics	37	92	129

[a] Anesthesia induction to standing recovery

The incidence of adverse reactions may be associated with preanesthetic, maintenance anesthetic, and/or duration of anesthesia. Average duration of anesthesia was approximately 47 minutes for cats maintained with isoflurane and 23 minutes for cats maintained with propofol.

Electrocardiogram (ECG) abnormalities:
Five cats each in groups 1, 2, and 3, eight in group 4, two in group 5, seven in group 6, four in group 7, and five in group 8 showed cardiac arrhythmias during anesthesia. Arrhythmias included supraventricular tachycardia (SVTs secondary to atropine administration are not included), atrial premature contractions (APCs), ventricular premature contractions (VPCs), sinus bradycardia, atrial ventricular dissociation, and sinus arrhythmia. The incidence of these arrhythmias was low during the study, and no unexpected safety concerns were identified when using propofol for induction or maintenance of anesthesia. Second degree atrioventricular block was present in 3 cats that received medetomidine preanesthesia.

Other significant findings on the cats' ECGs were changes in the ST segment and T waves. Fourteen cats in Group 1, seventeen cats in Group 2, sixteen cats in

Group 3, seventeen cats in Group 4, nineteen cats in Group 5, nineteen cats in Group 6, eighteen cats in Group 7, and nineteen cats in Group 8 had depression or elevation in their ST segment that occurred after induction. Since these changes occurred after the induction of anesthesia in all 8 treatment groups, they were most likely due to myocardial hypoxia as a result of anesthesia.

Adverse reactions outside (before or after) anesthesia are presented in Table 9. Eighty-two adverse reactions were recorded outside anesthesia. Fifty-eight (of 160) cats experienced at least 1 adverse reaction outside anesthesia.

Table 9: Number of Adverse Reactions Before or After Anesthesia in Cats

Preanesthetic	**Number of Adverse Reactions Outside Anesthesia[a]**		
	Propofol Maintenance	**Isoflurane Maintenance**	**Total**
No preanesthetic	7	4	11
Acepromazine + Butorphanol	11	7	18
Medetomidine	22	14	36
Midazolam + Butorphanol	9	8	17
All preanesthetics	49	33	82

[a] Before propofol induction or after standing recovery

11. Concomitant Treatments: One hundred fifty-one (of 160) cats received at least one concomitant treatment related to anesthesia, including (in order of frequency) intravenous fluid infusions (to prevent dehydration or hypotension, but also for therapeutic treatment of hypotension in several patients), supplemental heat, ophthalmologic products, topical lidocaine to suppress laryngospasm, supplemental oxygen, anti-inflammatory products, anticholinergics, local anesthetics, analgesics, and positive pressure ventilation.

Table 10: Number of Concomitant Treatments Administered During Anesthesia

Preanesthetic	**Number of Concomitant Treatments[a]**		
	Propofol Maintenance	**Isoflurane Maintenance**	**Total**
No preanesthetic	61	60	121
Acepromazine + Butorphanol	63	66	129
Medetomidine	56	54	110
Midazolam + Butorphanol	65	65	130
All preanesthetic groups	245	245	490

[a] Treatments administered during anesthesia

Concomitant treatments not related to anesthesia were administered to 126 (of 160) cats. In total, 305 treatments not related to the anesthetic period were

documented. The use of concomitant treatments was equally distributed across treatment groups.

12. Injection site: Three cats showed abnormalities at propofol injection sites: one with a moderately swollen paw, and two with mild swelling at the injection site. These abnormalities resolved. Four cats reacted during propofol injection. The reaction may have been indicative of pain. Two cats had a moderate reaction (one of these received extravascular propofol), and two had a mild reaction.

13. Clinical pathology: Abnormalities noted at baseline included elevated white blood cell counts, elevated liver enzymes, and elevated renal enzymes. None of the findings were determined to be clinically significant, and abnormal parameters improved or were normal after anesthesia.

Conclusions: This study demonstrated that propofol was effective and safe for induction and maintenance of anesthesia in cats that did not receive a preanesthetic, and in cats that received 0.025 mg/kg acepromazine and 0.2 mg/kg butorphanol, 10 mcg/kg medetomidine, or 0.2 mg/kg midazolam and 0.2 mg/kg butorphanol as a preanesthetic.

III. TARGET ANIMAL SAFETY (CATS):

A. Preanesthetic Compatibility Study

Study Title and Number: The anesthetic cardiovascular and respiratory compatibility of PROPOCLEAR when administered intravenously to cats premedicated with acepromazine, medetomidine, midazolam or butorphanol (Study 0989-F-US-03-05).

Type of Study: Preanesthetic compatibility (laboratory study)

Study Dates: March 6 to April 13, 2006

Study Director: William Muir, DVM, Ph.D.
Columbus, Ohio

General Design:

1. Purpose: To determine the dose of intravenously (IV) administered propofol necessary to induce anesthesia in cats that received acepromazine (a phenothiazine), medetomidine (an alpha$_2$-adrenoreceptor agonist), midazolam (a benzodiazepine), or butorphanol (an opiate) as a preanesthetic, and to document responses of cats to the drug combinations.

2. Description of Test Animals: The study utilized 36 purpose-bred, adult domestic short hair cats equipped with telemetry transmitters designed to measure and record direct arterial blood pressure, heart rate, electrocardiogram (ECG), and body temperature.

3. Treatment Groups: This study evaluated 6 treatment groups. The study was randomized and controlled. Control cats received 0.9% sterile saline.

Table 11: Preanesthetic Treatment Groups, Cats

Treatment Group	Preanesthetic Dose[a]	Number and Sex of Cats
1	Saline 0.2 ml/kg	3 male, 3 female
2	Acepromazine 0.05 mg/kg	3 male, 3 female
3	Acepromazine 0.1 mg/kg	3 male, 3 female
4	Medetomidine 10 mcg/kg	3 male, 3 female
5	Midazolam 0.2 mg/kg	3 male, 3 female
6	Butorphanol 0.4 mg/kg	3 male, 3 female

[a] Saline and preanesthetics administered IM into a rear leg muscle approximately 25 minutes before IV propofol induction dose administration.

The study utilized a parallel design with 3 female and 3 male cats assigned to each of the 6 treatment groups. Each cat was subjected to a single anesthetic episode.

4. Dosage Form: 1% w/v propofol microemulsion intravenous injectable (commercial formulation).

5. Administration: Propofol was administered once, to effect (until the cat was anesthetized to allow placement of an endotracheal tube), with a maximum dose not to exceed 9.0 mg/kg. The dose was administered over a period of up to 60 seconds through an in-dwelling intravenous catheter.

6. Variables Measured: The study included physical examinations, serum chemistry and hematology, body weights, and once daily observations. For the anesthetic episodes, the study recorded the preanesthetic and propofol doses and times of administration, time to onset of lateral recumbency, time to onset of anesthesia, duration of apnea (if observed), time to responsiveness to noxious stimuli, end of anesthesia (time extubated), time cats regained sternal recumbency, overall anesthetic score, and observations of adverse events. Physiological responses documented during anesthesia included blood pressure (systolic, diastolic, mean arterial pressure), heart rate, body temperature, electrocardiogram, respiration rate, and blood oxygenation level by pulse oximetry (SpO_2). Physiological variables were assessed at predetermined times relative to the start of propofol administration. A dose sparing ratio was calculated for each treatment group by dividing the mean propofol dosage (mg/kg) of each preanesthetic treatment group by the mean of the saline control group.

7. Statistical Methods: The above variables were summarized by treatment group as mean, standard deviation, minimum, and maximum.

   Results: All 36 cats completed the study. The mean propofol dosage required to anesthetize cats in the control group (pretreated with saline) was 6.24 mg/kg. The

propofol dosage range in the control group was 5.32 to 9.23 mg/kg. The 1 cat in this group treated with 9.23 mg/kg received an initial dose of propofol followed by a second dose to facilitate intubation. Due to this protocol deviation, the results presented below exclude the dosing data from this cat; however, the results do include the safety data from this cat. There was no dose sparing effect with either preanesthetic dose of acepromazine or butorphanol.

Table 12 summarizes the propofol dosing times, duration of anesthesia, and duration of recumbency for each treatment group. With the exception of cats that received the 10 mcg/kg medetomidine preanesthetic, mean duration of anesthesia ranged from approximately 13 to greater than 19 minutes; mean duration of anesthesia for cats premedicated with 10 mcg/kg medetomidine was 41 minutes. Treatment-related patterns in duration of recumbency were similar to patterns noted in duration of anesthesia. The overall anesthetic scores for all groups were considered optimum. There was no evidence of pain during intravenous administration of PROPOCLEAR.

Table 12: Mean Propofol Dosing and Anesthesia Parameters[a], Cats

	Treatment Group					
Variable Measured	**1[e]**	**2**	**3**	**4**	**5**	**6**
Propofol Dose (mg/kg)	5.64	5.61	5.76	4.89	5.37	6.09
Propofol Dosing Time[b]	0:39	0:37	0:36	0:35	0:36	0:38
Time to Onset of Anesthesia	0:58	1:19	1:04	1:06	1:09	1:03
Duration of Anesthesia[c]	13:13	16:46	14:30	40:52	19:13	18:40
Time to Noxious Stimuli Score ≥ 2	14:19	18:00	19:23	51:52	30:07	16:35
Duration of Recumbency[d]	0:23:37	0:25:01	0:23:42	1:05:40	0:39:29	0:24:21
Dose Sparing Ratio	1.00	0.99	1.02	0.87	0.95	1.08

[a] All times are recorded at min:sec or hr:min:sec
[b] Elapsed interval between propofol administration start and end times
[c] Elapsed interval from intubation to extubation
[d] Elapsed interval from lateral recumbency during induction until sternal recumbency during recovery
[e] Excludes 1 cat not dosed according to the protocol.

All treatment groups experienced a reduction in mean heart rate, mean respiratory rate, and mean blood oxygen saturation (SpO_2) following propofol administration. The medetomidine group had the greatest decline in mean heart rate after administration of propofol (from 197 bpm prior to administration to 107 bpm at 25 minutes after propofol administration) followed by the butorphanol group (from 199

bpm prior to administration to 131 bpm at 20 minutes after propofol administration). The other groups had mean heart rates similar to the control (saline) group. The groups that received midazolam or butorphanol experienced the greatest declines in mean respiratory rate. The change in SpO_2 was similar among all groups and no cats experienced apnea during the study.

Adverse reactions attributed to PROPOCLEAR in this study were consistent with known effects of propofol. Two cats had SpO_2 values decline below 85% after propofol administration (1 cat from the saline group and 1 cat from the butorphanol group). SpO_2 declined below 85% within 2-3 minutes after the start of the propofol administration. The values recovered to greater than or equal to 85% by 5 minutes after the start of propofol administration. Two cats had mean arterial pressure (MAP) decline below 50 mmHg after receiving propofol (1 cat from the 0.10 mg/kg acepromazine group and 1 cat from the butorphanol group). Mean arterial pressure fell below 50 mmHg within 1-3 minutes after the start of propofol administration, but recovered to values greater than 50 mmHg by 6 minutes after the start of the propofol administration. Four cats exhibited sinus arrhythmia following propofol administration (1 cat in the saline group, 1 cat in the medetomidine group, and 2 cats in the midazolam group). Another cat in the medetomidine group exhibited a sinus arrhythmia following preanesthetic administration that continued after propofol administration. Other clinical observations included nystagmus, muscle twitching, paddling, stretching, torticollis, opisthotonus, and limb movements.

Conclusions: This study demonstrated that PROPOCLEAR was effective and safe for induction of anesthesia in cats that did not receive a preanesthetic, or received 0.05 mg/kg acepromazine, 0.10 mg/kg acepromazine, 10 mcg/kg medetomidine, 0.2 mg/kg midazolam or 0.4 mg/kg butorphanol. The most common adverse reactions following the propofol induction dose included SpO_2 values below 85% and mean arterial pressure (MAP) values below 50 mmHg. There were no unexpected adverse interactions between propofol and the preanesthetic products used in this study.

B. Multi Dose Safety Study

Study Title and Number: Target Animal Safety of a Novel Aqueous Nano-droplet Formulation of Propofol Administered to Cats **(**Study Number 0989-F-US-02-05**).**

Type of Study: GLP Laboratory Study

Study Dates: January 16 to February 11, 2006

Study Director: Theodore J. Baird, Ph.D.
Mattawan, MI

General Design:

1. Purpose: To evaluate the safety and potential toxicity of a 1% w/v propofol microemulsion when administered intravenously (IV) to cats.

2. Description of Test Animals: The study utilized 24 purpose-bred, domestic short hair cats, aged 6.5 to 7 months and weighing 2.34 to 4.25 kg on Study Day 0. All cats were surgically instrumented with venous and arterial vascular access ports (VAP) for

arterial blood collection and venous drug administration, and with radiotelemetric devices for remote measurement of electrocardiogram, heart rate, direct arterial blood pressures (systolic, diastolic and mean), and body temperature.

3. Treatment Groups: Cats were randomly assigned to 1 of 3 treatment groups.

Table 13: Treatment Groups, Cats

Group	Treatment	Induction Dose	Maintenance Doses & No. of doses	Number of Animals	
				Male	Female
0X	Sterile Saline	1.2 mL/kg	0 0 doses	4	4
1X	PROPOCLEAR	8.0 mg/kg	Up to 4.4 mg/kg 3 doses	4	4
1.5X	PROPOCLEAR	12.0 mg/kg	Up to 4.4 mg/kg 6 doses	4	4

4. Dosage Form: Propofol microemulsion, 1% w/v (10 mg/mL), commercial formulation.

5. Drug Administration: The entire induction dose was administered as a slow bolus injection over 90 seconds. Induction doses were given in total and not "to effect." Maintenance doses were administered when the cat showed signs of swallowing and were given until anesthetic effect was achieved (maximum of 4.4 mg/kg per maintenance dose). The cats in the 1X group received 3 maintenance doses and the cats in the 1.5X group received 6 maintenance doses on each treatment day. Cats in the 0X group received a single injection of 0.9% sterile saline at 1.2 mL/kg (volume equal to the dose for the 1.5X group) on each treatment day, but did not receive maintenance doses. Cats were treated every other day for a total of 6 treatment days.

6. Route of Administration: Doses were administered via an IV catheter placed in the cephalic vein prior to the time of dosing on Day 0 and Day 10 (first and last day of treatment), and through the venous access port (VAP) on all other days.

7. Variables Measured: Variables measured during the study included physical examinations, body temperature, body weight, food consumption, daily observations, pain on injection, heart rate, respiratory rate, electrocardiogram, arterial blood gases

(pH, pCO_2, pO_2, HCO_3, tCO_2, MetHb), blood pressure (systolic, diastolic, mean arterial), hematology, serum chemistry, urinalysis, coagulation, necropsy, and histopathology of pre-selected tissues, including injection sites. Physiological variables were assessed at predetermined times relative to the start of propofol administration. Anesthesia variables included duration of anesthesia for the induction and maintenance doses, time to swallow reflex, time to extubation, and time to head control. If an adverse reaction occurred, the time relative to dose administration, and duration of the adverse reaction were recorded.

8. Statistical Methods: When appropriate, data were analyzed using a repeated measures analysis (separately on each day) with treatment, sex, time, and all interactions included as fixed effects. When available, a pretreatment value was included as a covariate. All effects involving treatment were evaluated at α=0.1. Any significant findings was also evaluated for clinical relevance.

   Anesthesia duration for induction and maintenance doses and recovery times were reported as mean, minimum and maximum. Results for each treatment group were presented for males, females, and both sexes combined. Anesthesia time was calculated as [time to swallowing reflex – induction time] while recovery time was calculated as [time to head control – extubation time].

Results:

Twenty-two cats completed the study. One cat in the 1.5X group died on Study Day 0 after administration of the second maintenance dose. This cat developed propofol-induced cyanosis, followed by apnea, hypoxemia, hypotension, bradycardia, arrhythmias, and death. The second death was not related to propofol (euthanized on Day 6, 1.5X group).

Anesthetic Duration: The duration of induction dose anesthesia was dose-dependent (3-times longer for 1.5X group), as shown in Table 14 below. Once both propofol-treated groups began the maintenance phase of doses given "to effect," mean anesthesia duration following maintenance doses was similar between the 1X and 1.5X dose groups, and generally remained within the approximate range of 5-25 minutes (typical values between 10 and 15 minutes duration).

The mean doses based on mg/kg of body weight used for maintenance anesthesia were similar for the 1X group and the 1.5X group (2.89 mg/kg and 2.73 mg/kg respectively) for all study days combined. Because the maintenance doses were given "to effect," there was a widely variable range of doses for individual animals within both treated groups (0.96 mg/kg to 4.75 mg/kg).

There was a sex related effect for duration of anesthesia in the propofol treated groups. Female cats had shorter mean anesthesia time after induction than male cats in the 1X group (5-6 minutes for females and 9-10 minutes for males) and the 1.5X group (19-20

minutes for females and 24-25 minutes for males). The reason for this sex effect is unknown.

Table 14: Duration of Induction, Maintenance and Total Anesthesia[a], All Days Combined, Cats

Dose		1X Dose Group (3 maintenance doses)			1.5X Dose Group (6 maintenance doses)		
		Males	Females	Combined	Males	Females	Combined
Induction[b]	**Mean**	0:09:12	0:05:40	**0:07:26**	0:24:04	0:19:05	**0:21:27**
	Min	0:00:16	0:01:05	0:00:16	0:10:48	0:03:28	0:03:28
	Max	0:45:49	0:29:40	0:45:49	0:39:45	0:41:53	0:41:53
Maintenance[b]	**Mean**	0:14:24	0:15:17	**0:14:51**	0:13:06	0:14:55	**0:14:04**
	Min	0:00:21	0:02:40	0:00:21	0:01:23	0:04:08	0:01:23
	Max	0:41:33	0:50:05	0:50:05	0:53:38	0:44:06	0:53:38
Total	**Mean**	0:58:13	0:58:02	**0:58:37**	1:56:13	2:02:08	**1:59:24**
	Min	0:18:51	0:24:54	0:18:51	1:15:10	1:12:10	1:12:10
	Max	2:00:49	1:31:18	2:00:49	3:31:53	2:59:43	3:31:53

[a] Times presented in hrs:min:sec

[b] Induction and maintenance anesthesia durations do not include dose administration times

Anesthetic Recovery: There was large variability in individual recovery times (extubation to head control), ranging from 0 minutes to 1 hour in the 1X group, and 0 minutes to 57 minutes in the 1.5X group. Female cats had shorter mean recovery times than males on all 6 study days in the 1X group, and 4 of 6 study days in the 1.5X group. Mean recovery times did not increase with each subsequent anesthetic day, however, both treated groups had longer mean recovery times on most study days compared to Day 0.

Physiological Findings: Propofol produced dose-dependent decreases in respiratory rate, heart rate, arterial blood pressure, blood gases, and body temperature.

1. Respiratory rate: There was a significant decrease in respiratory rates after administration of the induction dose. Respiratory rates for the propofol treated groups remained lower than baseline and conscious 0X group values for nearly all post-dose recording intervals on dosing days.

2. Heart rate: Decreases in mean heart rate from pre-treatment baseline values and values in conscious 0X animals were approximately 40-60 beats/minute in the 1 X group and 65-85 beats/minute in the 1.5X group. Heart rate values returned to baseline within 1.5 to 3 hours in the 1X cats, and 2.5 to 3 hours in the 1.5X cats.

3. Arterial blood pressure: Propofol produced significant decreases in mean systolic, diastolic, and mean arterial pressures (MAP) on all treatment days in the 1X and 1.5X groups. The reduction in blood pressure occurred within minutes of dosing. Average systolic, diastolic, and MAP values decreased approximately 5-20% in the 1X group, and approximately 12-40% in the 1.5X group. Recovery to baseline arterial pressure values was generally related to the number of maintenance doses received.

4. Blood gas: The partial pressure of oxygen (pO_2) was consistently decreased immediately following induction at both dose levels on all treatment days. The

changes were similar on all treatment days and usually resolved by the end of the monitoring period. Similar but less consistent trends were seen with decreased oxygen saturation (sO_2) and pH, and concurrent increases of pCO_2.

5. Body temperature: Mean body temperatures decreased in a dose and time dependent manner in both treated groups. External heat sources were not used, and no attempts were made to correct decreases in body temperature. Cats in the 1X group had a maximal decrease in mean body temperature of 2.7- 4.5° F (1.5-2.5° C) from baseline, with values generally returning to baseline between 2-3 hours after the induction dose. Cats in the 1.5X group had a maximal decrease of 4.5-6.3° F (2.5-3.5° C) from baseline, with many cats not returning to baseline temperature at 3 hours after the induction dose (end of monitoring period).

Repeat administration of PROPOCLEAR did not affect body weights, clinical chemistry, coagulation, or urinalysis. Red blood cell indices in all 3 groups decreased during the study. This was considered secondary to repeat blood collection, and not a result of propofol administration. Heinz body formation was not noted.

Clinical Findings: The most frequent clinical observations included salivation, decreased respiratory rate, and pale mucous membranes. Twitching was observed once in one high-dose cat, and tremors were seen once in another high-dose cat. Propofol was administered on the first and last study days through peripheral IV catheters, and pain on injection was not observed on those treatment days. On the other 4 treatment days, propofol was administered through VAPs, and 1 cat in the control group and 1 cat in the 1X group experienced pain on injection.

Necropsy and Histopathology: The saline and propofol-treated groups had findings consistent with venipuncture from intravenous catheters (hemorrhage and inflammation) at the injection sites. A thrombus at the injection/catheter sites was observed in 4 cats (2 from the 1X and 2 from the 1.5X group). Minimal tubular degeneration or degeneration/regeneration was noted on histopathology of the kidney in 4 cats (1 male and 1 female in both the 1X and 1.5X groups).

Adverse Reactions: Protocol-defined adverse reactions (AR) included pale mucous membranes, cyanosis, apnea (no voluntary inspiratory effort for > 60 seconds), hypotension (mean arterial blood pressure ≤ 50 mmHg), bradycardia (heart rate ≤ 50 beats per minute), arrhythmias, and death. The following tables list the number of times each AR occurred during the entire study and on each study day. If they occurred, adverse reactions were counted once per anesthetic episode per cat, and some cats

experienced more than one AR with each anesthetic episode. There were 89 anesthetic episodes during the study (48 for 1X group, 41 for 1.5X group).

Table 15: Total Adverse Reactions (AR) for the 1X and 1.5X Groups[a], Cats

Adverse Reaction	Number of AR		Percent of Total AR	No. of cats with AR[b]
	1X	1.5X		
Pale mucous membranes	13	16	43.2%	10/16
Hypotension	1	13	20.9%	8/16
Arrhythmia	4	8	17.9%	9/16
Cyanosis	1	4	7.5%	5/16
Apnea	2	3	7.5%	5/16
Bradycardia	0	1	1.5%	1/16
Death	0	1	1.5%	1/16
Total	**21**	**46**	**100%**	**14/16**

[a] Adverse reactions that occurred during a total of 89 anesthetic episodes
[b] Total of 8 cats per group

Table 16: Adverse Reactions (AR) by Study Day for the 1X Group[a], Cats

Adverse Reaction	Study Day							No. of cats with AR
	0	2	4	6	8	10	Total	
Pale mucous membranes	3	2	3	2	1	2	**13**	5/8
Hypotension	1	0	0	0	1	0	**1**	1/8
Arrhythmia	1	1	0	1	1	0	**4**	3/8
Cyanosis	0	0	0	0	1	0	**1**	1/8
Apnea	0	0	1	0	1	0	**2**	2/8
Bradycardia	0	0	0	0	0	0	**0**	0/8
Death	0	0	0	0	0	0	**0**	0/8
Total	**5**	**3**	**4**	**3**	**4**	**2**	**21**	7/8

[a] There were 48 anesthetic episodes during the study for Group 1X

Table 17: Adverse Reactions (AR) by Study Day for the 1.5X Group[a], Cats

Adverse Reaction	Study Day							No. of cats with AR
	0	2	4	6	8	10	Total	
Pale mucous membranes	3	4	3	3	1	2	**16**	5/8
Hypotension	2	4	3	1	1	2	**13**	7/8
Arrhythmia	4	3	1	0	0	0	**8**	6/8
Cyanosis	4	0	0	0	0	0	**4**	4/8
Apnea	2	0	0	1	0	0	**3**	3/8
Bradycardia	1	0	0	0	0	0	**1**	1/8
Death	1	0	0	0	0	0	**1**	1/8
Total	**17**	**11**	**7**	**5**	**2**	**4**	**46**	7/8

[a] There were 41 anesthetic episodes during the study for Group 1.5X

Adverse reactions occurred most commonly after administration of the induction dose, often within the first few minutes after dosing.

Pale mucous membranes occurred following induction and maintenance dose administration in the 1.5X group, and after maintenance dose administration in the 1X group. Cyanosis was observed most commonly during induction dose administration, and was seen primarily in the 1.5X dose group. Hypoxemia, acidosis, and hypercapnia were observed in cats that experienced cyanosis.

Two cats in the 1X group and 3 cats in the 1.5X group had episodes of apnea. With the exception of 1 cat, apnea occurred within 1 minute of propofol administration after both induction and maintenance doses. All cats except one received positive pressure ventilation (PPV) and the 3 cats having the longest durations of apnea were given supplemental oxygen. One cat in the 1.5X group developed cyanosis after maintenance dose 1, and apnea within the first minute of maintenance dose 2 administration. Despite respiratory support and an intravenous saline bolus, hypoxemia, profound hypotension, bradycardia, arrhythmias, and death followed.

There was a dose-dependent increase in the number of hypotensive episodes caused by propofol. Hypotension occurred 13 times in 7 cats from the 1.5X group, during or immediately following administration of the induction dose. Hypotension occurred once in 1 cat from the 1X group and did not require intervention. All 7 hypotensive cats in the 1.5X group received epinephrine as a vasopressive agent during each of the 13 hypotensive episodes. Following epinephrine administration, the 1.5X group cats had a rebound increase in MAP, therefore the duration of hypotension was approximately 1 minute or less. Arrhythmias occurred in 5 of 7 hypotensive cats that received propofol and epinephrine, and included AV block, junctional or ventricular rhythms, ST segment elevation, supraventricular tachycardia, atrial standstill with ventricular escape rhythm, and wide QRS complexes. Two cats had ECG abnormalities without experiencing hypotension. Arrhythmias in these 2 cats included one premature ventricular contraction, large T-waves, and an idioventricular rhythm. Arrhythmic cats experienced concurrent adverse reactions such as hypotension, apnea, cyanosis, and pale mucous membranes.

Conclusions:
Under the conditions of the study, propofol administered at 8.0 mg/kg (induction dose), and up to 4.4 mg/kg (maintenance dose given to effect) safely induced and maintained anesthesia in cats. Adverse reactions included pale mucous membranes, cyanosis, apnea, hypotension, and arrhythmias. When propofol was administered at 12.0 mg/kg (induction dose) and up to 4.4 mg/kg (maintenance dose given to effect) additional adverse reactions occurred, including bradycardia and death in 1 cat.

IV. GENERAL INFORMATION (Dogs):

A. File Number: NADA 141-303

B. Sponsor: Fort Dodge Animal Health, Division of Wyeth, a wholly owned subsidiary of Pfizer Inc.
235 East 42nd St., New York, NY 10017

Drug Labeler Code: 000856

C. Proprietary Name(s): PROPOCLEAR

D. Established Name(s): Propofol

E. Pharmacological Category: Anesthestic

F. Dosage Form(s): Microemulsion

G. Amount of Active Ingredient(s): 10 mg/mL

H. How Supplied: 20 mL sterile multi-dose vial
50 mL sterile multi-dose vial
100 mL sterile multi-dose vial

I. How Dispensed: Rx

J. Dosage(s):

Induction of General Anesthesia in Dogs: Induction dose guidelines are 4.0 - 6.5 mg/kg in dogs that do not receive a preanesthetic, and 1.4 - 6.5 mg/kg in dogs that receive a preanesthetic. The mean PROPOCLEAR induction dose is reduced by 20-30% for dogs that receive a preanesthetic (dose sparing effect). Anesthesia is usually observed within 60 seconds after the end of the induction dose administration. Duration of anesthesia following the recommended induction dose is approximately 4 minutes without a preanesthetic and 4-11 minutes with a preanesthetic. Individual anesthesia times may vary. Induction doses for dogs given PROPOCLEAR alone or after a preanesthetic are indicated in the following table. The table is for guidance only. The actual induction dose should be based on patient response.

PROPOCLEAR (10 mg/mL) Induction Dose Guidelines: Dogs			
Preanesthetic	**Mean Induction Dose (mg/kg)**	**Induction Dose Range (mg/kg)**	**Induction Dose Sparing**

Phenothiazine + Opioid	4.4	1.9 – 6.5	29%
Alpha$_2$-adrenoreceptor agonist	4.5	1.5 – 6.5	27%
Benzodiazepine + Opioid	4.9	1.4 – 6.5	20%

Maintenance of General Anesthesia in Dogs: Anesthesia can be maintained by administration of PROPOCLEAR using intermittent IV injections. For dogs, the duration of anesthesia following a PROPOCLEAR maintenance dose is approximately 3-5 minutes. Clinical response may vary, and is determined by the dose, the rate of administration, and the frequency of maintenance injections. The maintenance dose and frequency should be based on the patient's response. Sighthounds may need lower maintenance doses of PROPOCLEAR, and the time between maintenance dose administration and for recovery may be longer. The table below is provided for guidance.

PROPOCLEAR Maintenance Dose Guidelines: Dogs		
Preanesthetic	**Mean Maintenance Dose (mg/kg)**	**Maintenance Dose Range (mg/kg)**
None	1.8	0.7 – 3.0
Phenothiazine + Opioid	1.8	0.4 – 3.3
Alpha$_2$-adrenoreceptor agonist	1.8	0.7 – 2.3
Benzodiazepine + Opioid	1.7	0.7 – 3.3

Inhalant Anesthetic Maintenance of General Anesthesia in Dogs: Additional low doses of PROPOCLEAR, similar to a maintenance dose, may be required to facilitate the transition to inhalant maintenance anesthesia.

K. Route(s) of Administration: Intravenous injection

L. Species/Class(es): Dogs

M. Indication(s): For the induction and maintenance of anesthesia and for induction followed by maintenance with an inhalant anesthetic, in cats and dogs.

V. EFFECTIVENESS (DOGS):

Dosage characterization for the dog was determined using a precursor formulation (TPI-213M) to the final market formulation PROPOCLEAR. The products differed only in the inactive ingredients used to preserve the formulation. The percent of active ingredient was identical for both formulations.

A. Dosage Characterization:

Study Title and Number: Canine Pharmacokinetic Evaluation of TPI-213M (Study No. MDSPS 030214).

The biopharmaceutics/pharmacokinetics justification for selection of 6.0 mg/kg of PROPOCLEAR, administered over approximately 60 seconds, for induction and maintenance of general anesthesia in dogs is based upon a single-dose comparative bioavailability study of a precursor formulation (TPI-213M) of PROPOCLEAR and RAPINOVET. Six male Beagle dogs, weighing 7.7 – 11.5 kg, were administered 6.0 mg/kg of TPI-213M, administered over approximately 60 seconds, using a two-treatment, two-period crossover design. Whole blood and plasma propofol concentrations were determined. Propofol biopharmaceutics/pharmacokinetics based on whole blood samples were similar to biopharmaceutics/pharmacokinetics based on plasma samples. The table below summarizes the results of the study.

Table 18: Mean Pharmacokinetic Parameters for TPI-213M and RAPINOVET

Test Article	**Peak plasma concentration (C_{max}) (± 1SD)**	**Time of peak concentration (Tmax) (± 1SD)**	**$AUC_{0-\infty}$ (± 1SD)**	**Half-life (± 1SD)**
TPI-213M	5746 (1763) ng/mL	1 (0) minutes	928 (128) hours·ng/mL	0.4 (0.1) hours
RAPINOVET	8590 (5895) ng/mL	1 (0) minutes	1064 (269) hours·ng/mL	0.4 (0.3) hours

The estimated ratio for mean Cmax values (based on log-transformed data) of TPI-213M relative to RAPINOVET was 0.85 and the 90% Confidence Interval Limits about the ratio were 0.47 and 1.53. Similarly, for comparison of mean $AUC_{0-\infty}$ values the estimated ratio was 0.93 and the 90% Confidence Interval Limits about the ratio was 0.72 and 1.20. Therefore, the mean Cmax and $AUC_{0-\infty}$ values for the treatments are not equivalent, i.e., the 90% Confidence Interval Limits do not meet the criterion: 0.80 to 1.25.

The pharmacodynamics of TPI-213M and RAPINOVET treatments were assessed by investigator observation of key anesthetic events. The results showed differences in anesthetic events between treatments, such as time to sternal recumbency, but the time was shorter by 1.5 minutes with TPI-213M. In contrast, Cmax (whole blood or plasma) was about 10% less following TPI-213M than following RAPINOVET. For observations associated with the depth of anesthesia, such as time from dosing to eye movement or induced paw/tail movements, the times were longer and in rank order with larger exposure following RAPINOVET. Overall, the differences in pharmacodynamic observations were not consistent with differences in bioavailability/pharmacokinetics of the products.

Conclusion: The dosage (6.0 mg/kg) was determined to be acceptable for evaluation of dosage characterization.

B. Substantial Evidence:

1. Dog Field Study

Study Title and Number: Multicentric Field Study to Investigate the Efficacy and Safety of 1% w/v Propofol injection in Dog Anesthesia (Study Number 0989-C-US-03-06).

Type of Study: Good Clinical Practices (GCP) field study

Study Dates: January 2007 to July 2007

Investigators and Locations:

Investigators	Location
Roger Sifferman, DVM Bert Shelley, DVM	Springfield, Missouri
Lynn Buzhardt, DVM Gwen Rutkowski, DVM	Zachary, Louisiana
David Hancock, DVM Kathleen Fish, DVM	Victor, New York
Mark Marks, DVM Kristi Rowland, DVM	Lawrence, Kansas
Jeff Williams, DVM Craig Kryger, DVM	Kinsman, Ohio
Jeff Williams, DVM Scott Smith, DVM	Middlefield, Ohio
Samuel Geller, VMD	Quakertown, Pennsylvania

General Design:

1. Purpose: To investigate the effectiveness and safety of 1% w/v propofol injection in dogs for anesthesia induction, induction followed by maintenance, and anesthesia induction followed by anesthetic maintenance with an inhalant anesthetic.

2. Description of Test Animals: One hundred sixty-one dogs enrolled in the study. Dogs were client owned and required general anesthesia for surgeries or short

procedures. Twenty-eight were neutered males, 40 were intact males, 53 were spayed females, and 40 were intact females at study enrollment. The age of dogs ranged from 3.3 to 12.9 years, with a mean age of 4.4 years. There were 117 purebred dogs, and the most represented breeds were Labrador Retriever (16.8%, 27 dogs), Greyhound (8.7%, 14 dogs) and Yorkshire Terrier (6.2%, 10 dogs). Mixed breed dogs were 27.3% (44 dogs) of the study population.

Pregnant or nursing dogs and dogs classified as ASA III or greater were not enrolled in the study. Dogs were fasted for at least 6 hours prior to anesthesia induction. One hundred and fifty-eight dogs were used for effectiveness evaluation, and all dogs were evaluated for safety. Based upon pretreatment physical examinations, patients were classified as follows according to the American Society of Anesthesiologist scoring system: 64.6% were ASA Class 1 (healthy) and 35.4% were ASA Class 2 (mild systemic disease).

3. Treatment Groups: Dogs were assigned to 1 of 8 treatment groups based on the dog's anesthetic requirement. All dogs received propofol for anesthesia induction.

Table 19: Preanesthetic and Anesthetic Treatment Groups, Dogs

Group	Preanesthetic	Maintenance
1	None	Propofol
2	None	Isoflurane
3	Acepromazine + Butorphanol	Propofol
4	Acepromazine + Butorphanol	Isoflurane
5	Medetomidine	Propofol
6	Medetomidine	Isoflurane
7	Midazolam + Butorphanol	Propofol
8	Midazolam + Butorphanol	Isoflurane

Preanesthetics were administered at the following dosages. The mean time from preanesthesia administration to propofol induction was 25:09 min:sec, with a range of 15:30 to 39:00 min:sec.

Table 20: Preanesthetic Dosages, Dogs

Preanesthetic	Dosage	Route of Administration
Acepromazine	0.05 mg/kg	IM
Medetomidine	0.01 mg/kg	IM
Midazolam	0.2 mg/kg	IM
Butorphanol	0.2 mg/kg	IM

4. Propofol Dosage Form: 1% w/v , microemulsion intravenous injectable (commercial formulation).

5. Administration: Propofol was administered through indwelling intravenous catheters over approximately 60 seconds. Propofol was administered once, to effect (until the dog was anesthetized to allow placement of an endotracheal tube), up to a maximum dose of 6.5 mg/kg. Additional doses of propofol were administered if clinically necessary to achieve intubation. Once intubated, anesthesia was maintained either with intermittent intravenous doses of propofol or the inhalant anesthetic isoflurane.

6. Variables Measured: The study included physical examinations, serum chemistry, hematology, body weights, and observations of animals for clinical signs. The following anesthetic variables were recorded during the study: the preanesthetic and propofol doses and times of administration, time to onset of lateral recumbency, time to onset of anesthesia, duration of apnea (if observed), end of anesthesia (time extubated), time to sternal recumbency, overall anesthetic score, and observations of adverse reactions. Physiological responses documented during anesthesia included indirect systolic blood pressure, heart rate, body temperature, electrocardiogram (ECG), respiration rate, and blood oxygenation level by pulse oximetry (SpO_2). Physiological variables were assessed at predetermined times relative to the start of propofol treatment. A dose sparing ratio was calculated for each preanesthetic treatment group by dividing the mean propofol dosage (mg/kg) of each preanesthetic treatment group by the mean propofol dosage of the group that did not receive a preanesthetic.

7. Statistical Methods: Effectiveness was assessed by examining time to onset of recumbency, onset of anesthesia, duration for anesthesia, duration of recumbency, time to standing recovery, and quality of anesthesia. Results were reported as mean, minimum and maximum, and were presented individually for males, females as well as combined for each treatment group.

8. Procedures: The most frequently performed procedures included dental cleaning/dental extractions or dental procedures with another surgical procedure (80/161 dogs); neutering or spaying (69 of 161 dogs); radiographs (6/161 dogs); and other surgical procedures such as mass removal (19/161 dogs).

9. Clinical Pathology Findings: Dogs enrolled in the study had blood and urine samples collected for hematology, serum chemistry, urinalysis, and coagulation times prior to study enrollment (baseline). Additional clinical pathology was performed after anesthesia, if the dog had clinically significant abnormalities at baseline. Clinical pathology abnormalities included elevated white blood cell counts, elevated liver enzymes, elevated renal enzymes, proteinuria, and mild thrombocytopenia. None of the findings were determined to be clinically significant, and were improved or normal on clinical pathology performed after anesthesia.

10. Results:

Induction of Anesthesia: The mean propofol induction dosage for dogs that did not receive a preanesthetic was 6.2 mg/kg. The mean propofol induction dosage for dogs that received preanesthetics was 4.6 mg/kg. The use of a preanesthetic produced a dose sparing effect for the propofol induction dosage. The propofol induction dosage for dogs that received a preanesthetic was reduced by 20-30%. An isoflurane dose sparing effect was seen in dogs that received a preanesthetic followed by propofol anesthesia induction. Isoflurane usage was reduced by 8 – 20%.

Table 21: Mean Propofol Induction Dosages by Treatment Group, Dogs

Group	**Preanesthetic**	**Propofol Induction Dosage (mg/kg)**		
		Mean	**Min.**	**Max.**
1	None	6.5	4.9	9.4
2	None	5.9	4.0	6.5
3	Acepromazine Butorphanol	4.7	2.7	6.5
4	Acepromazine Butorphanol	4.2	1.9	6.1
5	Medetomidine	4.9	2.0	6.5
6	Medetomidine	4.1	1.5	6.5
7	Midazolam Butorphanol	5.4	3.0	6.5
8	Midazolam Butorphanol	4.8	1.4	6.5

Maintenance of Anesthestia: Eighty dogs received propofol maintenance anesthesia, with 77 dogs receiving one or more propofol maintenance doses. The mean propofol maintenance dosage was 1.8 mg/kg for all groups. Administration of a preanesthetic and type of preanesthetic had no effect on the mean propofol maintenance dosage. The mean duration of maintenance dose anesthesia for all groups combined was 03:35 minutes:seconds (min:sec), with the non-preanesthetic group having a slightly shorter duration and the medetomidine group having a slightly longer duration. Sighthounds received a mean maintenance dosage of 1.3 mg/kg, with a mean duration of maintenance anesthesia of 04:43 min:sec (lower maintenance dosage with a longer duration).

Table 22: Summary of Effectiveness Data for Propofol Maintenance Anesthesia (Groups 1, 3, 5 and 7), Dogs

Variable Measured	Sight-hounds	All Dogs
Number of Dogs	6	80
Mean Propofol maintenance dose (mg/kg)	1.4[a]	1.8[b]
Mean Number of propofol maintenance doses	4.7	5.5[b]
Mean Duration of anesthesia by induction dose[c]	18:56	5:54
Mean Time interval between maintenance doses	4:43[a]	3:35[b]

[a] One dog did not require maintenance doses of propofol, so the mean is based on data from 5 dogs.
[b] Three dogs did not require maintenance doses of propofol; mean is based on 77 dogs.
[c] Elapsed interval (min:sec) from intubation to first maintenance dose (or extubation for dogs not requiring maintenance anesthesia)

Table 23: Mean Dosing and Anesthesia Parameters for All Treatment Groups, Dogs[a]

Variable Measured	Treatment Group							
	1	2	3	4	5	6	7	8
No. dogs	19	19	20	20	20	21	20	19
Propofol Dosing Time[b]	1:19	1:07	0:50	0:59	0:57	1:06	0:58	1:11
Time to Onset of Anesthesia	1:51	1:46	1:25	1:22	1:24	1:28	1:27	1:39
Duration of Anesthesia[c]	32:50	45:47	37:51	47:33	42:32	52:59	42:37	58:25
Duration of Recumbency[d]	45:07	50:00	55:12	57:28	1:01:11	1:06:07	53:59	1:06:21
Time to Standing Recovery[e]	19:25	11:48	37:39	27:51	31:15	28:17	23:54	16:41

[a] min:sec or hr:min:sec
[b] Elapsed interval between propofol infusion start and end times
[c] Elapsed interval from intubation to extubation
[d] Elapsed interval from lateral recumbency during induction until sternal recumbency during recovery
[e] Elapsed interval from extubation to standing recovery

Data comparing sighthounds to all dogs are summarized in Table 24. At 38:23 (min:sec), the average time to standing recovery in sighthounds was about 14 min longer than in the total dog population. Other data that compared sighthounds to the total population of dogs included duration of anesthesia and duration of recumbency.

Table 24: Summary of Effectiveness Data Comparing Sighthounds to All Dogs

Variable Measured	Sighthounds	All Dogs
Number of Dogs	16	159
Mean Time to onset of anesthesia (min:sec)	01:36	01:09
Mean Duration of anesthesia [a] (min:sec)	53:06	45:06
Mean Duration of recumbency [b] (hr:min:sec)	1:20:01	0:57:03
Mean Time to standing recovery [c] (min:sec)	38:23	24:49

[a] Elapsed interval from intubation to extubation
[b] Elapsed interval from lateral recumbency during induction until sternal recumbency during recovery
[c] Elapsed interval from extubation to standing recovery

Table 25 summarizes data from dogs in which anesthesia was maintained with propofol. The mean propofol maintenance dose was 1.77 mg/kg, for all treatment groups combined. There was minimal variation in mean propofol maintenance dosages between preanesthetic groups. The mean number of maintenance dose administered was 5.6 doses, with a mean range of 4.0 to 6.9 doses. The mean maintenance dosing interval for non-preanesthetic group dogs was 02:58 (min:sec), and for preanesthetic dogs was 03:08 to 4:47 (min:sec).

Table 25: Summary of Effectiveness Data for Propofol Maintenance Anesthesia

Variable Measured	Treatment Group			
	1	3	5	7
Number of Dogs	19	20	20	20
Mean Propofol maintenance dose (mg/kg)	1.8	1.8	1.8	1.7
Mean Number of propofol maintenance doses	6.5	4.8	4.0	6.9
Mean Time interval between maintenance doses (min:sec)	2:58	3:32	4:47	3:08

Table 26: Summary of Effectiveness Data for Propofol Maintenance Anesthesia Sighthounds and All Dogs

Variable Measured	Sighthounds in Groups 1, 3, 5 & 7	All Dogs in Groups 1, 3, 5 & 7
Number of Dogs	6	80
Mean Propofol maintenance dose (mg/kg)	1.4 [a]	1.8 [b]
Mean Number of propofol maintenance doses	5.8 [a]	5.6 [b]
Mean Time interval between maintenance doses (min:sec)	4:43 [a]	3:35 [b]

[a] One dog required no maintenance treatments, so the mean is based on data from 5 dogs.
[b] Three dogs required no maintenance treatments; mean is based on 77 dogs.
[c] Elapsed interval from intubation to first maintenance dose (or extubation for dogs not requiring maintenance anesthesia)

Anesthesia Scores: Table 27 summarizes Investigator assessment scores pertaining to quality of induction, maintenance and recovery for each treatment group.

Table 27: Summary of Quality of Anesthesia Score Frequencies for Induction, Maintenance and Recovery, Dogs

Anesthesia Phase	Treatment Group							
	1	2	3	4	5	6	7	8
Induction								
Excellent (%)	60.0	95.5	100.0	95.0	90.0	90.5	90.0	80.0
Acceptable (%)	40.0	5.0	0.0	5.0	10.0	9.5	10.0	20.0
Unacceptable (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Maintenance								
Excellent (%)	80.0	75.0	85.0	95.0	100.0	100.0	90.0	100.0
Acceptable (%)	20.0	25.0	15.0	5.0	0.0	0.0	10.0	0.0
Unacceptable (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Recovery								
Excellent (%)	95.0	85.0	70.0	60.0	90.0	85.7	85.0	75.0
Acceptable (%)	5.0	15.0	30.0	40.0	10.0	14.3	15.0	10.0
Unacceptable (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	15.0

Investigators scored induction and anesthesia quality as excellent or acceptable in 100% of dogs in all treatment groups. Recovery from anesthesia was scored as excellent or acceptable in 100% of dogs that did not receive a preanesthetic (Groups 1 and 2), that received phenothiazine + opioid (Groups 3 and 4), or alpha2-adrenoreceptor agonist (Groups 5 and 6), or a benzodiazepine + opioid and propofol maintenance anesthesia (Group 7). Recovery from anesthesia was scored excellent or acceptable in 85%, and unacceptable in 15% of dogs that received a benzodiazepine + opioid preanesthetic and isoflurane maintenance anesthesia (Group 8).

Table 28: Number of Concomitant Treatments Related to Anesthesia, Dogs

Preanesthetic	Number of Concurrent Treatments Related to Anesthesia		
	Propofol Maintenance	Isoflurane Maintenance	Total
No preanesthetic	49	43	92
Acepromazine + Butorphanol	56	60	116
Medetomidine	65	63	128
Midazolam + Butorphanol	62	49	111
All preanesthetics	232	215	447

Concomitant treatments not related to anesthesia were administered to 92.5% (149/161) of the enrolled dogs. In total, 443 treatments not related to anesthesia

were documented. The distribution of concomitant treatments was equal among treatment groups.

Electrocardiogram (ECG): ECG abnormalities increased after preanesthetic administration and after propofol induction, when compared to baseline. ECG abnormalities noted at baseline included Tall R-waves, tachycardia (SVT), ventricular premature contractions (VPC), paroxysmal atrial tachycardia (PAT), sinus arrest, rS (small R-wave, large S-wave), and second degree heart block. There was a 46% increase in the number of dogs with ECG abnormalities after propofol administration, when compared to baseline. ECG abnormalities reported after propofol administration and during anesthesia included Tall R-waves, VPC, atrial premature contractions (APC), PAT, SVT, sinus bradycardia, sinus arrest, first degree heart block, second degree heart block, sinus arrest, ventricular escape beats, and rS. Dogs that received medetomidine as a preanesthetic experienced a 27.6% to 48.3% increase in ECG abnormalities when compared to dogs that did not receive a preanesthetic, or received acepromazine + butorphanol or midazolam + butorphanol as a preanesthetic. If they occurred, VPC were more severe in the dogs that received medetomidine preanesthesia. Atropine was the only medication used to treat ECG abnormalities (bradycardia) that occurred during anesthesia.

Table 29: Number of Dogs with ECG Abnormalities

Group	Baseline (T – 45 min)	After Preanesthesia (T – 5 min)		Post Induction	
		Other	Atropine SVT[a]	Other	Atropine SVT[a]
1	1	1	3	7	3
2	2	1	4	5	2
3	4	15	2	7	3
4	7	3	5	7	1
5	6	11	7	14	0
6	6	14	4	15	1
7	2	2	5	3	6
8	1	5	2	5	3
Total	**29**	**52**	**32**	**63**	**19**

[a] Supraventricular tachycardia secondary to atropine administration

Adverse Reactions: Tables 30a and 30b and 31 summarize adverse reactions associated with anesthesia. These tables display the number of dogs in each

treatment group presenting with adverse reactions that occurred after preanesthesia but before propofol to after administration of the induction dose through the end of anesthesia. Compared to the population of non-preanesthetic dogs in Groups 1 and 2, the incidence of bradycardia (defined as heart rate ≤ 70 beats per minute or ≤ 60 bpm in giant breeds), was higher in all preanesthetized groups, both before and after propofol administration. Groups 3 and 4 (preanesthesia with acepromazine and butorphanol) had an increase the incidence of bradycardia during the pre-induction period, and following anesthetic induction with propofol. The incidence of abnormal ECGs among the population of dogs in Groups 3 and 4 (acepromazine and butorphanol) was higher than in the population of non-preanesthetized dogs.

Table 30a: Summary of Adverse Reactions for Groups 1-4, Dogs

Adverse Reaction	Group 1		Group 2		Group 3		Group 4	
	Before[a] Propofol	After Propofol	Before[a] Propofol	After Propofol	Before[a] Propofol	After Propofol	Before[a] Propofol	After Propofol
Abnormal ECG[b]	1	7	1	5	15	7	3	7
Apnea (> 60 sec)	0	0	0	1	0	0	0	3
Bradypnea (RR <10 bpm)	0	8	0	8	0	9	1	9
Bradycardia (≤ 70 bpm)	0	0	0	2	3	9	1	9
Hypertension (> 165 mm Hg)	1	5	5	3	0	2	3	0
Hypotension (≤ 70 mm Hg)	0	1	0	0	0	1	0	3
Hyperthermia (>104 °F)	0	0	0	1	0	0	1	0
Hypothermia (< 97 °F)	0	0	0	0	0	1	0	3
Hypoxia (SpO2 < 85%)	1	1	1	0	1	4	0	1
Pain on Injection	NA	3	NA	2	NA	0	NA	2
Tachycardia[c]	0	6	2	3	0	1	1	2

[a] Before findings are after preanesthetic medications were administered
[b] Excludes dogs that had atropine induced SVT
[c] Excludes dogs that received atropine during anesthesia

Dogs in Groups 5 and 6 (preanesthetized with medetomidine) experienced a higher incidence of bradycardia after medetomidine administration and after propofol preanesthesia. Bradycardia was documented in 14/41 dogs (34%) in Groups 5 and 6 prior to the start of propofol infusion, and 27/41 dogs (66%) following propofol administration. Bradycardia is an known effect of medetomidine in dogs, as well as cardiac arrhythmias, decreased respiration and hypothermia. Incidence of abnormal ECG in Groups 5 and 6 was higher than non-preanesthetized dogs. Twenty-four dogs (59%) in Groups 5 and 6 had abnormal ECG before propofol induction, and 27 dogs (65%) had abnormal ECG

after propofol induction. There were two non-preanesthetized dogs with abnormal ECG before propofol and twelve following propofol administration.

After administration of propofol, apnea occurred at least once during anesthesia in 6 dogs (3.7%). The incidence of hypotension was higher following induction of anesthesia with propofol than before induction. A total of 12 dogs (7.5%) experienced hypotension (systolic blood pressure ≤ 70 mm Hg) following propofol administration. The incidence of hypoxia, (SpO_2 < 85%) increased after propofol administration; 14 dogs (8.7%) experienced hypoxia following propofol administration versus 7 dogs before (4.3%). Because SpO_2 was measured using pulse oximetry, many of the observations of SpO_2 below 85% prior to induction of anesthesia with propofol were likely due to the difficulty of measuring SpO_2 in conscious animals. Apnea, hypotension and low SpO_2 are secondary to the cardio-respiratory depressive effects of propofol.

Table 30b: Summary of Adverse Reactions for Groups 5-8, Dogs

Adverse Reaction	Group 5		Group 6		Group 7		Group 8	
	Before[a] Propofol	After Propofol	Before[a] Propofol	After Propofol	Before[a] Propofol	After Propofol	Before[a] Propofol	After Propofol
Abnormal ECG[b]	11	14	14	15	2	3	5	5
Apnea (> 60 sec)	0	0	0	1	0	1	0	0
Bradypnea (RR <10 bpm)	1	14	1	15	0	7	1	7
Bradycardia (≤ 70 bpm)	5	10	9	17	0	4	1	4
Hypertension (>165 mm Hg)	5	8	4	6	2	2	3	5
Hypotension (≤ 70 mm Hg)	1	0	0	1	0	1	0	4
Hyperthermia (>104 °F)	0	1	0	0	0	0	0	0
Hypothermia (< 97 °F)	0	0	0	0	0	0	0	2
Hypoxia (SpO2 < 85%)	0	2	2	1	1	4	2	1
Pain on Injection	NA	2	NA	0	NA	2	NA	2[d]
Tachycardia[c]	1	1	1	1	0	2	2	4

[a] Before findings are after preanesthetic medications were administered
[b] Excludes dogs that had atropine induced SVT
[c] Excludes dogs that received atropine during anesthesia
[d] Includes one dog that had propofol extravasation

Table 31: Adverse Reaction for All Treatment Groups Combined, Dogs

Adverse Reaction (AR)	Number of AR After Preanesthetics	Number of AR After Propofol
Abnormal ECG[a]	52	63
Apnea (≥ 60 sec)	0	6
Bradypnea (< 10 bpm)	4	77[c]
Bradycardia (≤ 70 bpm)	12	90
Hypertension (> 165 mm Hg)	23	31
Hypotension (≤ 70 mm Hg)	1	12
Hyperthermia (> 104 °F)	1	2
Hypothermia (< 97 °F)	0	6
Hypoxia (SpO_2 < 85%)	7	14
Pain on Injection	0	13
Lack of Effectiveness	0	2
Tachycardia[b]	6	20

[a] Excludes dogs with atropine induced SVT (supraventricular tachycardia). At the baseline 29 dogs had abnormal ECGs.
[b] Excludes dogs that received an anticholinergic medication
[c] For isoflurane maintenance dogs, this only includes occurrences up to T+10

In two dogs (one no preanesthetic, Group 2, the other with medetomidine preanesthetic, Group 6), concerns regarding shallow depth of anesthesia led to concerns regarding effectiveness. Both animals were assigned to inhalant maintenance anesthesia, and in the non-preanesthetic Group 2 dog anesthesia was shallow starting 5 minutes after the start of propofol induction. In the Group 6 dog that received medetomidine preanesthetic, anesthesia was described as too light 2 minutes after the start of anesthesia. Because Investigators administered propofol to-effect, descriptions of light anesthesia in a total of 2/161 dogs were not unexpected.

The following table summarizes the adverse reactions recorded from administration of the propofol induction dose to extubation. Overall adverse reaction incidences were similar between non- preanesthetized and midazolam + butorphanol groups, slightly higher for the acepromazine + butorphanol groups. The medetomidine groups had a 33% to 48% increase in adverse reactions when compared to the other groups.

Table 32: Number of Adverse Reactions During Anesthesia[a], Dogs

Preanesthetic	Propofol Maintenance	Isoflurane Maintenance	Total
No preanesthetic	31	25	56
Acepromazine + Butorphanol	34	39	73
Medetomidine	52	57	109
Midazolam + Butorphanol	26	34	60
All preanesthetics	143	155	298

[a] From propofol induction to extubation

Frequencies of adverse reaction outside anesthesia are presented in Table 32. A total of 37.3% (60/161) of enrolled dogs experienced at least one adverse reaction outside anesthesia; a total of 90 adverse reactions were recorded outside anesthesia.

Table 33: Number of Adverse Reactions Outside of Anesthesia[a], Dogs

Preanesthetic	Propofol Maintenance	Isoflurane Maintenance	Total
No preanesthetic	2	7	9
Acepromazine + Butorphanol	16	11	27
Medetomidine	16	22	38
Midazolam + Butorphanol	10	6	16
All preanesthetics	44	46	90

[a] Before propofol induction or after standing recovery

These data suggest preanesthetics impacted the number of adverse reactions observed at times outside the interval following the start of propofol induction through the time animals were in standing recovery.

11. Concomitant Treatments: Concurrent treatments related to anesthesia were administered to 96.9% (156/161) of the enrolled dogs. Concurrent medications used during anesthesia included eye lubricant, atipamizole, carprofen, meloxicam, atropine, glycopyrrolate, doxapram, diphenhydramine HCl, and lidocaine 2% injectable. Concomitant treatments included intravenous fluids, supplemental oxygen, external heat source, and positive pressure ventilation. Concurrent treatments were used approximately equally on dogs in each group.

12. Injection Site: Only one reaction at an injection site was documented at the time of the post-anesthesia physical examination. The dog was one of two that experienced extravascular propofol administration during induction of anesthesia. The local reaction noted in this dog was not evident at the follow-up visit that occurred on Day 4 following treatment. One injection site reaction was noted during follow-up phone calls. The lesion was subsequently examined at the follow-up visit, and it was determined the lesion was not propofol related.

Conclusions: This study demonstrated that PROPOCLEAR was effective and safe for induction and maintenance of anesthesia in dogs that were not preanesthetized, or preanesthetized with 0.05 mg/kg acepromazine and 0.4 mg/kg butorphanol, 0.01 mg/kg (10 mcg/kg) medetomidine, or 0.2 mg/kg midazolam and 0.4 mg/kg butorphanol. Non-preanesthetized dogs received a mean of 6.2 mg/kg propofol to induce anesthesia. Apnea, hypotension and low SpO_2 were all observed following propofol administration. All of these effects are related to the known ability of propofol to cause cardio-respiratory depression.

VI. TARGET ANIMAL SAFETY (DOGS):

A. Preanesthetic Compatibility Study

Study Title and Number: The anesthetic cardiovascular and respiratory compatibility of propofol when administered intravenously to dogs premedicated with acepromazine, medetomidine, midazolam, or butorphanol (Study 0989-C-US-01-05).

Type of Study: Preanesthetic compatibility (laboratory study)

Study Dates: January 2 to February 23, 2006.

Study Director: William Muir, DVM, Ph.D.
Columbus, Ohio

General Design:

1. Purpose: To determine the dose of intravenously (IV) administered propofol necessary to induce anesthesia in dogs that received acepromazine (a phenothiazine), medetomidine (an $alpha_2$-adrenoceptor agonist), midazolam (a benzodiazepine), or butorphanol (an opiate) as a preanesthetic, and to document responses of dogs to the drug combinations.

2. Description of Test Animals: The study utilized 42 purpose-bred, adult Beagle dogs equipped with telemetry transmitters designed for direct blood pressure, heart rate, electrocardiogram (ECG), and body temperature measurements.

3. Treatment Groups: This study evaluated 6 treatment groups. The study was randomized and controlled. Control dogs received 0.9% sterile saline.

Table 34: Preanesthetic Treatment Groups, Dogs

Treatment Group	Preanesthetic Dosage [a]	Number and Sex of Dogs
1	Saline: 0.1 ml/kg	3 male, 3 female
2	Acepromazine: 0.11 mg/kg	3 male, 3 female
3	Acepromazine: 1.1 mg/kg	3 male, 3 female
4	Medetomidine 3.5 mcg/kg[b]	3 male, 3 female
5	Medetomidine: 34.5 mcg/kg[c]	3 male, 3 female
6	Midazolam: 0.2 mg/kg	3 male, 3 female
7	Butorphanol: 0.4 mg/kg	3 male, 3 female

[a] Saline and premedicants administered IM into a rear leg muscle approximately 25 minutes before IV propofol induction dose.
[b] Dosage range was 3.2 – 3.9 mcg/kg
[c] Dosage range was 31.9 – 37.9 mcg/kg

The study utilized a parallel design with 3 female and 3 male dogs assigned to each of the 7 treatment groups. Each dog was subjected to a single anesthetic episode.

4. Dosage Form: 1% w/v propofol microemulsion intravenous injectable (final market formulation).

5. Administration: Propofol was administered once, to effect (until the dog was anesthetized to allow placement of an endotracheal tube), up to a maximum dose of 7.0 mg/kg. The dose was administered over a period of 35 to 60 seconds through an in-dwelling intravenous catheter.

6. Variables Measured: The study included physical examinations, serum chemistry, hematology, body weights, and once daily observations. For the anesthetic episodes, the study recorded the preanesthetic and propofol doses and times of administration, time of onset of lateral recumbency, onset of anesthesia, duration of apnea (if observed), time to responsiveness to noxious stimuli, termination of anesthesia (time extubated), time dogs regained sternal recumbency, overall anesthetic score, and observations of adverse events. Physiological responses documented during anesthetic episodes included blood pressure (systolic, diastolic, mean arterial pressure [MAP]), heart rate, body temperature, electrocardiogram (ECG), respiration rate, and blood oxygenation level by pulse oximetry (SpO2). Physiological variables were assessed at predetermined times relative to the start of propofol treatment. A dose sparing ratio was calculated for each treatment group by dividing the mean dosing rate (mg/kg) of each preanesthetic treatment group by the mean of the saline control group.

7. Statistical Methods: The above variables were summarized by treatment group as mean, standard deviation, minimum, and maximum.

Results: Forty-two dogs completed the study. There was no dose sparing effect with 3.5 mcg/kg medetomidine dose and 0.2 mg/kg midazolam. Table 34 summarizes the propofol dosing times, duration of anesthesia, and duration of recumbency for each treatment group. With the exception of dogs preanesthetized with 34.5 mcg/kg medetomidine, duration of anesthesia ranged from approximately 4 to over 20 minutes; duration of anesthesia for dogs premedicated with 34.5 mcg/kg medetomidine ranged between 28 minutes to 1 hour 37 minutes. Treatment-related patterns in duration of recumbency were similar to patterns noted in duration of anesthesia. The overall anesthetic scores for all groups were considered optimum. There was no evidence of pain during intravenous injection of PROPOCLEAR.

Table 35: Mean Propofol Dosage and Anesthesia Parameters[a], Dogs

	Treatment Group						
Variable Measured	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Propofol Dose (mg/kg)	4.96	4.71	4.51	5.16	4.56	5.48	4.56
Propofol Dosing Time[b]	0:43	0:45	0:42	0:48	0:43	0:49	0:43
Time to Onset of Anesthesia	0:50	0:52	0:56	0:55	0:51	1:04	0:56
Duration of Anesthesia[c]	8:55	11:05	12:58	9:18	1:02:07	6:38	12:05
Time to Noxious Stimuli Score ≥ 2	6:51	10:54	12:42	9:11	1:21:30	7:51	12:14
Duration of Recumbency[d]	11:21	13:34	14:53	10:54	1:43:00	8:30	12:44
Dose Sparing Ratio	1.00	0.95	0.91	1.04	0.92	1.10	0.92

[a] All times are recorded at min:sec or hr:min:sec
[b] Elapsed interval between propofol infusion start and end times
[c] Elapsed interval from intubation to extubation
[d] Elapsed interval from lateral recumbency during induction until sternal recumbency during recovery

All treatment groups experienced a decrease in systolic blood pressure and SpO_2 after propofol administration. All groups, except the 34.5 mcg/kg medetomidine group, experienced a decrease in the mean MAP (mean arterial pressure), and diastolic blood pressure after propofol administration. The saline, 34.5 mcg/kg medetomidine, midazolam, and butorphanol groups experienced an increase in mean heart rate after propofol administration, followed by a decrease in heart rate. All dogs in the 34.5 mcg/kg medetomidine group experienced a low heart rate or protocol defined bradycardia (HR < 50 bpm) after preanesthetic administration, but before propofol administration. All dogs in the 34.5 mcg/kg medetomidine group experienced an increase in heart rate after propofol administration. In five dogs this occurred at the 5-minute observation time-point, and, for one dog this occurred at the 20-minute observation time-point. All dogs in this group returned to a low or bradycardic heart rate by the 25-minute observation time-point.

Adverse clinical reactions attributed to propofol treatment were consistent with the known effects of propofol. Every dog in the 34.5 mcg/kg medetomidine group and one dog in the midazolam group experienced protocol defined adverse reactions. Five of six dogs in the 34.5 mcg/kg medetomidine group experienced heart rates less than 50 beats

per minute (bpm) within 10 to 25 minutes after propofol administration. Bradycardia in these dogs lasted up to 1 hour and 50 minutes after propofol administration. Four of these dogs also had bradycardia at the observation period 5 minutes before propofol administration. One dog in the 34.5 mcg/kg medetomidine group experienced brief hypotension (MAP below 50 mmHg) and ST-segment depression on ECG at 2 minutes, with MAP returning to normal (71 mmHg) at 5 minutes post-dose. Another 34.5 mcg/kg medetomidine group dog experienced hypotension at 13 minutes after propofol administration, and returned to 123 mmHg at the 15-minute observation. Three dogs experienced a SpO_2 below 85% within 1 to 3 minutes of propofol administration (2 dogs in the 34.5 mcg/kg medetomidine dose group and 1 in the midazolam group). The SpO_2 returned to normal by the 5-minute observation time-point. Two dogs in the 34.5 mcg/kg medetomidine group experienced one episode of no respiratory effort lasting 40 seconds. The episodes occurred at 37 seconds and 1 minute 20 seconds after propofol dosing, and did not require intervention. The episodes were not accompanied by a decrease in SpO_2 or MAP. Other clinical observations noted during anesthesia or recovery included nystagmus, muscle twitching, paddling/limb movement, panting, shallow breathing, and tail wagging.

Conclusions: This study demonstrated that PROPOCLEAR was effective and safe for induction of anesthesia in dogs that did not receive a preanesthetic, or received 0.11 mg/kg acepromazine, 1.1 mg/kg acepromazine, 3.5 mcg/kg medetomidine, 34.5 mcg/kg medetomidine, 0.2 mg/kg midazolam, or 0.4 mg/kg butorphanol. Dogs in the 34.5 mcg/kg medetomidine group had much longer anesthesia and recovery times compared to the other groups. The main adverse reactions following propofol administration occurred in the 34.5 mcg/kg medetomidine group, and included SpO_2 values below 85%, MAP values below 50 mmHg, heart rates below 50 bpm, and transient apnea. There were no unexpected adverse interactions between PROPOCLEAR and the preanesthetic treatments selected for testing in this study.

B. Multi Dose Safety Study

Study Title and Number: Target Animal Safety of a Novel Aqueous Nano-droplet Formulation of Propofol Administered to Dogs. Study 0989-C-US-02-05**.**

Type of Study: GLP Laboratory Study

Study Dates: October 17 to November 12, 2005

Study Director: Theodore J. Baird, Ph.D.
Mattawan, MI

General Design:

1. Purpose: To evaluate the safety and potential toxicity of a 1% w/v propofol microemulsion propofol when administered intravenously (IV) to dogs.

2. Description of Test Animals: The study utilized 24 purpose-bred Beagle dogs, aged 7.5 to 8.5 months old, weighing 10.0 to 12.4 kg on Study Day 0. All dogs were instrumented with radiotelemetric devices for remote collection of electrocardiogram, heart rate, direct blood pressures (systolic, diastolic and mean), and body temperature. All dogs were surgically instrumented with vascular access ports for arterial blood collection.

3. Treatment Groups: Dogs were randomly assigned to treatment groups, and study participants were masked to treatment group assignment during the in-life phase of the study. The control group (0X) received 0.9% sterile saline, USP. The 1X and 3X groups received the entire PROPOCLEAR induction and maintenance doses every other day for 6 doses. Dogs were not dosed to effect. The entire induction dose was administered, and the entire maintenance dose was administered when the dog began to swallow.

Table 36: Treatment Groups, Dogs

Group	Treatment	Induction Dose	Maintenance Doses	Number of Animals	
				Male	Female
0X	Sterile Saline	2.1 mL/kg	NA	4	4
1X	PROPOCLEAR	7.0 mg/kg	3.3 mg/kg (3 doses)	4	4
3X	PROPOCLEAR	21.0 mg/kg	3.3 mg/kg (6 doses)	4	4

4. Dosage Form: Propofol microemulsion, 1% w/v (10 mg/mL).

5. Route of Administration: The entire induction or maintenance dose was administered through a peripheral intravenous catheter. Doses were initially administered over 1 minute, but due to the death of two dogs on Study Day 0, the dose administration time was increased to 2 minutes. Maintenance doses were administered when the dog showed signs of swallowing.

6. Variables Measured: Variables measured during the study included physical examinations, body temperature, body weight, food consumption, daily observations, pain on injection, heart rate, respiratory rate, electrocardiogram, arterial blood gases (pH, pCO_2, pO_2, HCO_3, tCO_2, MetHb), blood pressure (systolic, diastolic, mean arterial), hematology, serum chemistry, urinalysis, coagulation, necropsy, and histopathology of pre-selected tissues, including injection sites. Physiological variables were assessed at predetermined times relative to the start of propofol administration. Anesthesia variables included duration of anesthesia for the induction and maintenance doses, time to swallow reflex, time to extubation, and time to head control. If an adverse reaction occurred, the time relative to dose administration, and duration of the adverse reaction was recorded.

7. Statistical Methods: When appropriate, data was analyzed using a repeated measures analysis (separately on each day) with treatment, sex, time, and all interactions included as fixed effects. When available, a pretreatment value was included as a covariate. All effects involving treatment were evaluated at $\alpha=0.1$. Any significant findings were also evaluated for clinical relevance.

   Anesthesia duration for induction and maintenance doses and recovery times were reported as mean, minimum and maximum. Results for each treatment group were presented for males, females, and both sexes combined. Anesthesia time was calculated as [time to swallowing reflex – induction time] while recovery time was calculated as [time to head control – extubation time].

Results:

Twenty-two dogs completed the study. One dog in the 3X group (21 mg/kg) died after administration of the induction dose on Study Day 0, and one dog in the 1X group (7 mg/kg) died after administration of the second maintenance dose on Study Day 0. Both dogs developed propofol-induced apnea, followed by hypotension, bradycardia, hypoxia, arrhythmias, and death. In response to the deaths, the administration duration of PROPOCLEAR was increased from 1 minute to 2 minutes on Study Days 2, 4, 6, 8 and 10.

Anesthetic Findings: Duration of induction and maintenance anesthesia time was dose dependent, with the 3X (21.0 mg/kg) group experiencing longer anesthesia times. The 1X males had greater mean induction, maintenance, and total anesthetic durations compared to 1X females. Recovery times were longer in the 3X group.

Table 37: Duration of Induction, Maintenance and Total Anesthesia[a], All Days Combined

Dose		1X Dose Group			3X Dose Group		
		Males	Females	Combined	Males	Females	Combined
	Mean	0:22:17	0:14:24	0:17:46	0:41:10	0:36:29	0:38:23
Induction	**Min**	0:05:59	0:04:26	0:04:26	0:25:28	0:14:37	0:14:37
	Max	0:37:39	0:22:33	0:37:39	0:53:03	0:58:28	0:58:28
	Mean	0:18:14	0:12:34	0:14:59	0:13:01	0:13:01	0:13:01
Maintenance	**Min**	0:03:57	0:01:44	0:01:44	0:00:35	0:00:06	0:00:06
	Max	0:37:19	0:25:00	0:37:19	0:36:41	0:27:49	0:36:41
	Mean	1:23:00	0:58:23	1:09:19	1:55:42	2:06:29	2:01:43
Total	**Min**	0:24:59	0:22:22	0:22:22	0:16:12	1:17:01	0:16:12
	Max	2:01:39	1:28:31	2:01:39	3:03:52	2:47:28	3:03:52

[a] Times presented in hours:min:sec

Physiological Findings: Repeat administration of PROPOCLEAR did not affect body weights, organ weights, clinical chemistry, coagulation, or urinalysis. Heart rates increased initially after administration of PROPOCLEAR, followed by a decrease, then stabilization of the heart rate. Body temperature decreased in a dose and time dependent manner in both treated groups, and returned to normal within 4 hours post anesthesia, or sooner. Red blood cell indices decreased during the study, and reticulocyte counts increased during the study. This is considered secondary to repeat blood collection, and not a result of propofol administration.

Concurrent Treatments: Two 3X group dogs required administration of intravenous 0.9% saline to reverse hypotension (mean arterial pressure (MAP) less than 50 mm Hg). One dog required intravenous fluids on Study Days 0, 2, 4 and 6; the other dog required intravenous fluids on Study Days 4 and 6. Positive pressure ventilation (PPV) was initiated for one 1X dog and seven 3X dogs that experienced apnea during anesthesia. In addition to PPV, supplemental oxygen was administered to the 1X dog, and four of the 3X dogs for treatment of hypoxia.

Electrocardiogram (ECG) findings: Abnormal ECG findings in the 1X (7.0 mg/kg) dog that died included large T-waves, second-degree AV block, ventricular escape rhythm, and ventricular tachycardia. No other dogs in the 1X group experienced ECG abnormalities. Findings in the 3X (21.0 mg/kg) dog that died included sinus tachycardia, second degree AV block, ventricular escape rhythm, and complete AV block. One 3X dog experienced abnormal ECG findings, between 30 seconds and 4 minutes 30 seconds after induction dose administration. The ECG abnormalities included sinus tachycardia, large T-waves, second-degree AV block, followed by sinus arrest with slow ventricular escape rhythm, and then sinus rhythm with ST-segment elevation and large T-waves. The dog recovered without intervention. Large T-waves were noted in three other 3X group dogs 3 minutes after the induction dose administration.

Clinical Findings: Dogs remained clinically healthy during the study. There were no changes on hematology and serum chemistry attributable to PROPOCLEAR. There was no pain noted on Day 0 administration. On subsequent induction dose administrations five 3X and two 1X dogs experienced pain or vocalization one time each with injection of PROPOCLEAR. The seven surviving 3X dogs experienced bruising, swelling, lameness or pain in one or more limbs, secondary to extravasation of PROPOCLEAR.

Necropsy and Histopathology Findings: The saline and treated groups had findings consistent with repeat venipuncture (hemorrhage and chronic inflammation) at the injection sites. Thrombus formation and edema were present in the treated groups, and are most likely the result of PROPOCLEAR extravasation. Thrombus formation and edema did not occur in the saline group. No other necropsy or histopathology findings were attributable to PROPOCLEAR.

Adverse Reactions: Protocol-defined adverse reactions (AR) included hypotension, bradycardia, apnea, arrhythmias, and death. The following table lists the number of times each AR occurred. If they occurred, ARs were counted once per anesthetic episode per dog, although some dogs experienced more than one AR with each anesthetic episode. There were 86 anesthetic episodes during the study.

Table 38: Total Adverse Reactions (AR) in the 1X and 3X Groups, Dogs

	Number of AR		**Percent of**
Event	**1X**	**3X**	**Total AR**
Pale mucous membranes	3	29	40
Apnea	1	24	31
Hypotension	1	11	15
Bradycardia	2	4	7.5
Arrhythmia	1	2	4
Death	1	1	2.5
Total	9	71	100 %

Table 39: Adverse Reactions for the 1X and 3X Groups by Study Day, Dogs

	Study Day						
Adverse Reaction	**0**	**2**	**4**	**6**	**8**	**10**	**Total**
Pale mucous membranes	7[ab]	5	5[b]	5	5	5	**32**
Apnea	3[a]	4	6	4	4	4	**25**
Hypotension	5[a]	2	2	1	1	1	**12**
Bradycardia	3[a]	0	0	1	0	2[b]	**6**
Arrhythmia	2[a]	0	0	1	0	0	**3**
Death	2[a]	0	0	0	0	0	**2**
Total	**22**	**11**	**13**	**12**	**10**	**12**	**80**

[a] Includes 1X dog that died
[b] Includes 1X dog

Adverse reactions occurred most often after induction dose administration. Pale mucous membranes and apnea usually occurred during dose administration or within two minutes of completing dose administration. All occurrences of apnea were treated with positive pressure ventilation (PPV), and oxygen was administered if there was clinical or blood gas evidence of hypoxia. Mean time from end of dose administration to onset of apnea was 58 seconds, and the mean duration of apnea was 22 minutes (range 1 - 55 minutes). Apnea occurred in one 1X dog, and seven 3X group dogs. Apnea in the 1X dog occurred after administration of the second maintenance dose. Six of the seven 3X dogs experienced apnea on more than one day, and one of the dogs died. All episodes of apnea in the 3X group occurred after induction dose administration. Two dogs experienced hypotension, and temporarily received intravenous fluids during anesthesia on more than one treatment day.

Conclusions:
Under the conditions of the study where the entire dose was administered, propofol 1% w/v administered for anesthesia induction (7.0 mg/kg) and maintenance (3.3 mg/kg) was safest when dose administration occurred over a 2-minute interval. Adverse reactions included apnea, pale mucous membranes, hypotension, bradycardia, and arrhythmias. Tachycardia and hypertension may occur in association with apnea, low respiratory rates, hypoxemia and acidosis, pale mucous membranes, and arrhythmias. Difficulty breathing and retching immediately after extubation occurred infrequently. Propofol may cause pain on injection, and swelling or bruising, if extravasation occurs.

VII. HUMAN FOOD SAFETY:

This drug is intended for use in cats and 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.

VIII. USER SAFETY:

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

Not for human use. Keep out of reach of children. Injection of this drug in humans may be associated with fatalities. PROPOCLEAR should be managed to prevent the risk of diversion, through such measures as strict restriction of access and the use of drug accountability procedures appropriate to the clinical setting. Exercise extreme caution to avoid accidental self-injection. In case of human injection, consult a physician immediately and provide the physician with the vial or the package insert/product information. Overdose is likely to cause cardiorespiratory depression (e.g., hypotension, bradycardia and/or apnea). 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 cases 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 technical assistance, to report a suspected adverse reaction, or to obtain an MSDS, call 1-800-533-8536.

IX. 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 PROPOCLEAR, when used according to the label, is safe and effective for the induction and maintenance of anesthesia and induction followed by maintenance with gas 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 expertise is required to properly administer the product and monitor the patient during anesthesia.

B. Exclusivity:

Under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval.

C. Patent Information:

PROPOCLEAR is under the following U.S. patent numbers:

U.S. Patent Number	Date of Expiration
7,550,155	October 2, 2023

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

X. ATTACHMENTS:

Facsimile Labeling:
Package insert
20 mL vial
50 mL vial
100 mL vial
20 mL carton
50 mL carton
100 mL carton