# FREEDOM OF INFORMATION (FOI) SUMMARY

# FOR

# PROPOFLO™ (propofol)

# ANESTHETIC INJECTION FOR DOGS

# NADA 141-098

**Abbott Laboratories**
**Animal Health Products**
**1401 Sheridan Road**
**North Chicago, IL 60064**

**PROPOFLO™**

**FREEDOM OF INFORMATION (FOI) SUMMARY**

**TABLE OF CONTENTS**

## FREEDOM OF INFORMATION SUMMARY

**1. General Information:**
**A. NADA 141-098**

**B. Sponsor:**
Abbott Laboratories
Animal Health Products
1401 Sheridan Road
North Chicago, IL 60064-4000

**C. Generic Name:**
Propofol

**D. Trade Name:**
PropoFlo™

**E. Marketing Status:**
Rx

**2. Indications for Use:**

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

**3. Dosage Form, Route of Administration and Recommended Dosages:**
PropoFlo is a stable emulsion containing 10 mg propofol per mL. It is available in 20 mL fliptop vials and is intended for intravenous use only.

**a. Induction of General Anesthesia**

For induction, propofol injection should be titrated against the response of the patient over 30-60 seconds or until clinical signs show the onset of anesthesia. Rapid injection of propofol (≤5 seconds) may be associated with an increased incidence of apnea (Smith *et al*., 1993).

The average induction dose ranges and dosage rates for healthy dogs given propofol alone, or when propofol is preceded by a premedicant, are indicated in the table below. The table is for guidance only. In practice, the dose should be based upon patient response.

Induction Dosage Guidelines

| *Preanesthetic* | *Propofol Induction Dose* | *Propofol Rate of Administration* | | |
|---|---|---|---|---|
| | *mg/kg* | *Seconds* | *mg/kg/min* | *mL/kg/min* |
| None | 5.5 | 40-60 | 5.5-8.3 | 0.55-0.83 |
| Acepromazine (Ace) | 3.7 | 30-50 | 4.4-7.4 | 0.44-0.74 |
| Ace/Oxymorphone (Oxy) | 2.6 | 30-50 | 3.1-5.2 | 0.31-0.52 |
| Xylazine (Xyl) /Butorphanol (But) | 3.1 | 30-50 | 3.7-6.2 | 0.37-0.64 |
| Diazepam (Diaz)/Oxy | 2.4 | 30-50 | 2.9-4.8 | 0.29-0.48 |
| Diaz/But | 3.3 | 30-50 | 4.0-6.6 | 0.40-0.66 |

The following average dosages of tranquilizers, sedatives, or analgesics administered as preanesthetic medications have been used in combination with propofol and may be lower than the label directions for their use as a single medication (Plumb, 1995).

The safety of general anesthesia with propofol when used in conjunction with butorphanol premedication was evaluated. However, butorphanol is not approved as a preanesthetic in dogs.

| | *Mean (Range) (mg/kg)* | *Routes* |
|---|---|---|
| Ace | 0.060 (<0.01-0.53) | IM, SC, IV |
| Oxy | 0.090 (0.04-0.20) | IM, SC, IV |
| Xyl | 0.33 (<0.01-0.69) | IM, SC |
| But | 0.33 (<0.01-0.71) | IM, SC, IV |
| Diaz | 0.21 (0.04-0.45) | IM, IV |

The use of these drugs as preanesthetics reduces propofol requirements. As with other sedative hypnotic agents, the amount of opioid, $\alpha$-2 agonist, and/or benzodiazepine premedication will influence the response of the patient to an induction dose of propofol.

In the presence of premedication, the dose of propofol is reduced with increasing age of the animal. The dose of propofol should always be titrated against the response of the patient.

During induction, additional low dose(s) of propofol, similar to those used for maintenance anesthesia with propofol, may be required to facilitate intubation or the transition to inhalant maintenance anesthesia.

**b. Maintenance of General Anesthesia**

Anesthesia can be maintained by administering propofol in intermittent IV injections. Clinical response will be determined by the amount and frequency of maintenance injections. The following table is provided for guidance:

Maintenance Dosage Guidelines

| *Preanesthetic* | *Propofol Maintenance Dose* | *Rate of Administration* | | | *Duration of Anesthesia* |
|---|---|---|---|---|---|
| | *mg/kg* | *Seconds* | *mg/kg/min* | *mL/kg/min* | *min* |
| None | 2.2 | 10-30 | 4.4-13.2 | 0.44-1.32 | 3.59-4.23 |
| Ace | 1.6 | 10-30 | 3.2-9.6 | 0.32-0.96 | 3.70-4.26 |
| Ace + Oxy | 1.8 | 10-30 | 3.6-10.8 | 0.36-1.08 | 5.05-6.51 |
| Xyl + But | 1.8 | 10-30 | 3.6-10.8 | 0.36-1.08 | 5.05-6.51 |
| Diaz + But | 1.8 | 10-30 | 3.6-10.8 | 0.36-1.08 | 5.05-6.51 |

Repeated maintenance doses of propofol did not result in increased recovery times or decreased dosing intervals, indicating that the anesthetic effects of propofol are not cumulative.

**4. Dose Rationale:**

Doses for propofol induction and maintenance were obtained from two Abbott feasibility studies and multiple sources in the literature. The proposed guidance induction dose was 6.0 mg/kg IV; a guidance maintenance dose of 1.3-1.6 mg/kg IV every 3 to 5 minutes was recommended. The same sources showed that preanesthetics may reduce the required propofol induction dose. Satisfactory induction and maintenance anesthesia were confirmed in the clinical field trial (discussed in detail in the Effectiveness section of the FOI Summary).

1. Abbott Feasibility Study I

A total of 12 mixed-breed research dogs (6 males and 6 females) were induced with Abbott propofol, and maintained with intermittent bolus injections while dentistries were performed or the animals were groomed. Propofol was injected "to effect" for induction of anesthesia over a 30 to 60 s period. In nine of the dogs, bolus doses were given to maintain a depth of anesthesia adequate for completion of the procedure.

The average induction dose for these mixed-breed dogs was 5.3 mg/kg (range of 3.6 to 7.8). All but two of the 12 dogs were successfully intubated after a single injection of propofol. The dogs maintained with propofol received an average of 8.4 doses (range of 5 to 14 doses); the average duration of anesthesia was 33.4 min (range of 15 to 57 min). The average maintenance dose was 1.3 mg/kg (range of 0.9 to 2.1 mg/kg). The first maintenance dose was administered an average of 6 min after the start of the induction dose (range of 3 to 8 min). The average interval between subsequent maintenance doses ranged from 3.4 to 4.7 min with no consistent pattern evident. These data indicate that propofol does not accumulate during periods of short-duration anesthesia.

Recoveries were complete (standing) in less than 15 min from the last injection of propofol (range of 7.8 to 20 min). Qualitative assessments of induction, maintenance and recovery were Excellent in 10 of 12 animals.

2. Abbott Feasibility Study II

A total of 34 mature Beagles (14 males and 20 females) were induced to anesthesia with propofol, and maintained with intermittent bolus injections while routine dentistries were performed. Half of the dogs received acepromazine (Ace; 0.03 mg/kg IM) prior to induction and the other half received no preanesthetic. Propofol was injected "to effect" for induction of anesthesia over a 30 to 60 s period. Bolus doses were given to maintain an adequate depth of anesthesia in order to complete the dentistry procedure. In 12 of the unpremedicated and 15 of the premedicated animals, maintenance of anesthesia was achieved through intermittent bolus injection of propofol. Procedures on the other animals did not require maintenance anesthesia.

Premedication with Ace reduced the dose of propofol required for intubation by approximately 40% (7.3 vs. 4.4 mg/kg). Except for one dog, intubation was accomplished within 1 min of the start of induction. Two of the premedicated dogs required additional propofol immediately after intubation due to panting or inadequate depth of anesthesia.

Unpremedicated and premedicated dogs received, respectively, an average of 2.1 and 2.2 maintenance doses of propofol. The interval from the start of induction to the first maintenance injection (M1) of propofol was only slightly increased by Ace; no other differences in maintenance intervals were observed between premedicated and unpremedicated animals. The average maintenance dose was 1.3 mg/kg (range of 0.7 to 2.1 mg/kg) without pre-medication and 1.0 mg/kg (range of 0.5 to 1.6 mg/kg) in premedicated animals.

In general, recoveries were uneventful. Times to various recovery events were influenced by Ace premedication. Time to extubation, sternal recumbency and standing recovery were prolonged on the average by, respectively, 1.6, 4.4 and 7.7 min in premedicated dogs.

3. Literature Sources:

The following table was compiled from information reported in published studies and shows over 200 dogs that were induced with propofol in the absence of a premedicant and over 475 dogs that were induced with propofol following the administration of a premedicant.

| **Preanesthetic**[a] | **NO PREANESTHETIC** | | **WITH PREANESTHETIC** | | **Reference** |
|---|---|---|---|---|---|
| | **number** | **Propofol** | **number** | **Propofol** | |

| | **of dogs** | **dose (mg/kg)** | **of dogs** | **dose (mg/kg)** | |
|---|---|---|---|---|---|
| acepromazine (0.05) + atropine (0.02) Maintenance by infusion | - | - | 30 | 4.9 | Hall & Chambers (1987) |
| acepromazine (0.02-0.04) + atropine (0.02) Maintenance by bolus dosing | 68[b]<br>5[d] | 5.9±1.9<br>5.2±1.4 | 12[c]<br>5[d] | 3.8±2.1<br>2.8±0.6 | Watkins, et al. (1987) |
| acepromazine + atropine (diazepam or xylazine in a few cases) | ≥39 | 6.6±1.7 | ≥208 | 4.5±1.5 | Morgan & Legge (1989) |
| acepromazine (0.05) + atropine (0.02) and opioid | 17<br>17 | 5.2±2.3<br>8.2 ± 3.3[e] | 69<br>70 | 3.6 ± 1.4<br>5.2 ± 2.7[e] | Weaver & Raptopoulos (1990) |
| acepromazine (0.1)<br>acepromazine (0.05) + atropine (0.05) and opioid | 4<br>- | 6.9 ± 0.9<br>- | 12<br>8 | 4.3 ± 1.3<br>2.2 ± 0.2 | Geel (1991) [non-elective surgery] |
| acepromazine (0.1)<br>acepromazine (0.05) + atropine (0.05) and opioid | 5<br>- | 4.1 ± 0.9 | 3<br>10 | 3.5 ± 1.2<br>2.9 ± 1.1 | Geel (1991) [elective surgery] |
| acepromazine (0.05) | 35 | 3.8 ($ED_{50}$)[f] | 25 | 2.2 ($ED_{50}$) | Watney & Pablo (1992) |

| | | | | | |
|---|---|---|---|---|---|
| none | 8<br><br>10 (grey-hounds) | 5.4<br><br>5.3 | -<br><br>- | -<br><br>- | Zoran & Riedesel (1993) |
| acepromazine (0.025) + atropine (0.02) | -<br><br>- | -<br><br>- | 7<br><br>6 (grey-hounds) | 3.2 ± 0.1<br><br>4.0 ± 0.3 | Robertson, et al. (1992) |

[a] dose in mg/kg if reported
[b] 34 dogs; 68 occasions
[c] 9 dogs; 12 occasions
[d] five dogs anesthetized both with and without premedication
[e] Total dose: intubation dose plus small doses between intubation and gas anesthesia
[f] Median effective dose

**5. Effectiveness:**

The safety and effectiveness of propofol in clinical use, as well as the appropriate dosages, were described by the clinical field trial.

CLINICAL STUDY

**Sponsor Monitors**
Riemond H. Rippel, PhD
Marshall S. Beleau, DVM
Lisa M. Rehm, DVM
Animal Health Products
Abbott Laboratories
1401 N. Sheridan Road
North Chicago, IL 60064-4000

**Study Investigators/Sites**
William W. Muir III, DVM, PhD
Dept. Veterinary Clinical Sciences
Ohio State University
Columbus, OH 43210-1089

Keith R. Branson, DVM, MS
College of Veterinary Medicine
University of Missouri
Columbus, MO 65211

Sandee M. Hartsfield, DVM, MS
Veterinary Teaching Hospital
Texas A & M University
College Station, TX 77843-4457

David Brunson, DVM
School of Veterinary Medicine
University of Wisconsin-Madison
Madison, WI 53706-1102

## STUDY OBJECTIVES

The objectives of the clinical investigation were to determine the effective dose of propofol, with and without preanesthetics, and evaluate its safety as an intravenous anesthetic agent in client-owned dogs when used for a) induction of anesthesia, b) maintenance of general anesthesia for up to 20 minutes or c) induction of general anesthesia where maintenance is provided by inhalant anesthetics.

## STUDY DESIGN

Treatment groups were selected to reflect routine veterinary clinical practice and included those preanesthetics and inhalant anesthetics most often used by veterinarians in private practice. The safety of general anesthesia with propofol when used in conjunction with butorphanol premedication was evaluated. However, butorphanol is not approved as a preanesthetic in dogs. Animals were assigned to anesthetic protocol (treatment group) according to patient needs. Groups 1, 2, 8, 9 and 10 included only patients requiring general anesthesia for anticipated short procedures of ≤20 min (e.g., physical exams, radiography, biopsy, endoscopy, minor surgery, etc.). Groups 3 through 7 included patients requiring procedures generally longer than 20 min and the use of an inhalant for maintenance of anesthesia. WI used Diaz + Oxy as a preanesthetic combination (Group 5A) rather than Xyl + But (Group 5 at the other sites).

Animals served as their own controls per 21 CFR 514.111(a)(5)(ii)(a)(2)(iii); baseline data was obtained on animals prior to treatment with any drug under the protocol. Only descriptive statistics were obtained on the data. Treatments could not be compared statistically since animals were not randomly assigned to treatment groups.

Propofol Maintenance

| *Treatment Group* | *Preanesthetic* | *Induction* | *Maintenance* | *N* |
|---|---|---|---|---|
| 1 | None | Propofol | Propofol | 49 |
| 2 | Acepromazine | Propofol | Propofol | 48 |
| 8 | Ace + Oxy | Propofol | Propofol | 16 |
| 9 | Xyl +But | Propofol | Propofol | 16 |
| 10 | Diaz + But | Propofol | Propofol | 16 |

Gas Inhalant Maintenance

| *Treatment Group* | *Preanesthetic* | *Induction* | *Maintenance* | *N* |
|---|---|---|---|---|
| 3 | None | Propofol | Isoflurane | 52 |
| 4 | Ace + Oxy | Propofol | Isoflurane | 54 |
| 5 | Xyl + But | Propofol | Isoflurane | 46 |
| 5A | Diaz + Oxy | Propofol | Isoflurane | 13 |
| 6 | Diaz + But | Propofol | Isoflurane | 53 |
| 7 | Ace + Oxy | Propofol | Halothane | 56 |

## MATERIALS AND METHODS

**Animals** A total of 419 dogs of American Society of Anesthesiologists (ASA) status I, II or III requiring general anesthesia for surgical or nonsurgical procedures were enrolled. Patients that were pregnant or had received an investigational drug within 30 d were excluded. No limitation was placed on breed, age or gender of the patient. Details of enrollment are provided below:

Number: 419
Breed: Forty-eight breeds were represented. Other than dogs of mixed breed (n=98), Labrador Retrievers (n=55), Greyhounds (n=25) and Golden Retrievers (n=24) were most frequently represented.
Age: Age distribution ranged from 0.2 to 16 yr. Mean age varied from lows of 3.0 and 3.3 yr in Groups 7 (Ace + Oxy/Hal) and 5 (Xyl + But/Iso), to a high of 7.2 yr in Groups 8 (Ace + Oxy/Prop) and 3 (None/Iso). Older dogs tended to be assigned to Groups 5A (Diaz + Oxy) and 6 (Diaz + But). Groups 2 (Ace) and 4 (Ace + Oxy) were intermediate in mean age at 5.2 and 4.5 yr, respectively.
Weight: Weight distribution ranged from 1.3 to 72.6 kg body weight. Mean group weights and distribution were similar among all treatments and ranged from a low of 18.0 to a high of 26.1 kg.
Sex: 205 males and 214 females
Health Status: ASA classification breakdown was: ASA I, n=193; ASA II, n=193 and ASA III, n=33. A total of two ASA II's and 20 ASA III's were classified as compromised. Sixteen of the 22 compromised patients were assigned to Groups 1 and 3 (no preanesthetic treatment).
Surgical Procedures: The individual or combination medical/surgical procedures performed on the dogs are grouped into the following major categories: Surgical/Invasive, n=228; Non-surgical/Minimally Invasive, n=113; and Diagnostic/Non-Invasive, n=78. The most prevalent procedures were dentistry (n=61), ovariohysterectomy (n=35), castration (n=32), radiography (n=24), endoscopy (n=22), biopsy (n=19), gastroscopy (n=18) and mass removal (n=14). Major invasive/surgical procedures (e.g. ovariohysterectomies, total hip replacements, cruciate repairs) involving pain totaled 111. The diagnostic/non-invasive procedures were heavily represented in Group 1 (no

preanesthetic) and the surgical procedures were predominant in Groups 4, 5, 6 and 7 (preanesthetic(s) and inhalant maintenance). Non-surgical/minimally invasive procedures were prevalent in treatment Groups 2 and 3.

**Anesthetic Procedures**

Propofol administration: The induction dose of propofol was given to effect a level of anesthesia sufficient for endotracheal intubation as judged by muscle relaxation, level of consciousness and jaw tone of the patient. An injection time of 10-30 seconds was recommended in the protocol. If the first attempt at intubation failed due to inadequate muscle relaxation or unconsciousness, additional propofol was given.

Dogs assigned to treatments 1, 2, 8, 9 and 10 breathed either room air or supplemental oxygen after induction. In most cases, animals in these groups required additional doses of propofol to complete the anesthetic procedure. These maintenance doses were also given "to effect" and at the same volume within a patient, when possible.

Premedicants: Atropine or glycopyrrolate were optional for all treatment groups. Administration of preanesthetics was performed according to the clinical practice standards of each test facility. Dose ranges and routes of other premedicants are provided in the table below.

| | | *Dose(mg/kg)* | | |
|---|---|---|---|---|
| *Premedicant* | *N* | *Mean* | *Range* | *Route(s)* |
| Ace | 174 | 0.060 | 0.00-053 | IM, SC, IV |
| Oxy | 139 | 0.090 | 0.04-0.20 | IM |
| Xyl | 62 | 0.330 | 0.00-0.69 | IM, IV |
| But | 131 | 0.326 | 0.00-0.71 | IM, SC, IV |
| Diaz | 82 | 0.207 | 0.04-0.45 | IM, SC, IV |

Gas anesthetic: Dogs assigned to treatments 3 through 7 were connected to the appropriate vaporized inhalant anesthetic immediately after intubation. A precision out-of-circle vaporizer and an in-circle $CO_2$ absorbent were used in the rebreathing systems. In general, the animals were allowed to breathe spontaneously during the procedure and, if hypoventilation occurred, controlled or assisted ventilation was provided and recorded.

**Variables Measured or Observed**

Anesthetic Dose: The amount and time of each dose of propofol was recorded. Time of injection for the induction dose was also recorded for 232 animals. In Groups 3-7, vaporizor concentrations and flow rates were also recorded at the beginning of maintenance and at each change of their levels.

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

Physiological: Arterial blood pressure (BP), respiratory rate (RR), core body temperature, end-tidal $CO_2$ and percent oxygen (hemoglobin) saturation were recorded at specified times before and during the procedure. The Investigator recorded all side effects observed throughout the study for specified time intervals. Particular attention was paid to, but not limited to, cardiorespiratory, musculoskeletal, gastrointestinal, central nervous system, ocular and behavioral phenomena. Frequency and duration of apnea were documented.

**RESULTS**

**Anesthetic Dose:**

Induction: Since the induction protocol was identical for Groups 1 and 3 (no preanesthetics); 4, 7 and 8 (Ace + Oxy); 5 and 9 (Xyl + But); and 6 and 10 (Diaz + But), a combined mean induction dose was computed for each group (see table below). Each of the premedicants and/or combinations markedly reduced propofol requirements.

| *Treatment Groups* | *Preanesthetic(s)* | *N* | *Total Dose (mg/kg)* | *Range (mg/kg)* |
|---|---|---|---|---|
| 1 + 3 | None | 101 | 5.5 | 2.0-16 |
| 2 | Ace | 48 | 3.7 (67%)* | 1.7-7.9 |
| 4 + 7 + 8 | Ace + Oxy | 126 | 2.6 (47%) | 0.7-6.1 |
| 5 + 9 | Xyl + But | 62 | 3.1 (56%) | 0.4-8.8 |
| 6 + 10 | Diaz + But | 69 | 3.3 (60%) | 1.3-6.7 |
| 5A | Diaz + Oxy | 13 | 2.2 (44%) | 0.3-3.6 |
| *percent propofol dose relative to no preanesthetics (Groups 1 + 3) | | | | |

The mean injection rates (mg/kg/min) for combined treatment groups are provided in the table below. In this study, the injection rate had no impact on dose or incidence of apnea. Also, the interval from injection of preanesthetic to induction had minimal effect on the mean induction dose (mg/kg) or on the injection rate (mg/kg/min).

| *Treatment Groups* | *Preanesthetic(s)* | *N* | *Injection Time (s)* | | *Injection Rate (mg/kg/min)* | |
|---|---|---|---|---|---|---|
| | | | *Mean* | *Range* | *Mean* | *Range* |
| 1 + 3 | None | 68 | 53.0 | 14-670 | 8.1 | 0.7-24.4 |
| 2 | Ace | 33 | 38.6 | 15-80 | 5.8 | 2.6-10.0 |
| 4 + 7 + 8 | Ace + Oxy | 58 | 38.8 | 15-120 | 4.5 | 0.9-14.4 |
| 5 + 9 | Xyl + But | 31 | 51.5 | 25-190 | 5.2 | 0.7-13.9 |
| 6 + 10 | Diaz + But | 35 | 46.7 | 16-130 | 4.8 | 0.7-11.3 |
| 5A | Diaz + Oxy | 8 | 30.9 | 15-71 | 3.9 | 0.7-7.9 |

The dose of propofol required for intubation was not affected by age of the patient when no preanesthetic was administered (Groups 1 + 3). However, a lower induction dose of propofol was required in older dogs given a single or a combination of preanesthetics (all other groups). In the groups with preanesthetics, approximately 11 to 18% less propofol

was required to induce dogs >10 yr of age compared to dogs <10 yr of age, as shown below.

| *Age (yr)* | *Mean Induction Dose (mg/kg)* *Treatments 1 & 3* | *All Others* |
|---|---|---|
| <1 | 5.5 | 3.1 |
| 1 - <5 | 5.8 | 3.2 |
| 5 - <10 | 5.0 | 3.0 |
| >10 | 5.7 | 2.7 |

A gender effect on the induction dose of propofol was evident when no preanesthetic was administered in that males required less drug (4.8 mg/kg; n=47) than females (6.1 mg/kg; n=54). When a preanesthetic(s) was administered, gender had no effect on the dose of propofol for induction (males, 3.0 mg/kg, n=158: females, 3.1 mg/kg, n=160).

The duration of anesthesia following induction with propofol can be obtained from the mean interval from the start of induction to the first maintenance dose of propofol (Groups 1, 2, 8, 9 and 10), as shown in the table, below. Although slightly longer in Group 9 (Xyl + But), the duration of anesthesia was generally similar between premedicated and unpremedicated animals.

| *Treatment Group* | *Preanesthetic* | *N* | *Duration of Anesthesia Following Induction (minutes)* *Mean* | *Range* |
|---|---|---|---|---|
| 1 | None | 47 | 6.2 | 1.3-18.0 |
| 2 | Ace | 47 | 5.7 | 0.8-15.0 |
| 8 | Ace + Oxy | 16 | 7.2 | 1.6-13.0 |
| 9 | Xyl + But | 16 | 10.4 | 1.9-18.0 |
| 10 | Diaz + But | 15 | 6.9 | 2.0-16.0 |

Maintenance with Propofol: The mean duration of anesthesia in Groups 1, 2, 8, 9 and 10 was, respectively, 29.2, 29.7, 32.8, 58.7 and 31.2 min. The longer duration of anesthesia in Group 9 (Xyl + But) was the result of a few lengthy procedures at one of the two sites (OH). The average number of propofol doses administered during maintenance ranged from 7.0 (Groups 8 and 10) to 9.0 (Group 1).

The interval between maintenance doses of propofol is summarized below for the first 10 injections. The intervals between doses were similar in dogs given no preanesthetic or Ace (Groups 1 and 2, respectively), whereas the interval was greater in those patients given a combination of preanesthetics. The interval between doses did not increase from early to late maintenance, indicating that propofol does not accumulate and that the drug's properties do not change with repeated administration.

Interval (min) Between Successive Doses of Propofol During Maintenance

| | *Group 1* | | *Group 2* | | *Groups 8, 9, 10* | |
|---|---|---|---|---|---|---|
| *Interval* | *n* | *Mean* | *n* | *Mean* | *n* | *Mean* |
| 1 | 40 | 4.04 | 42 | 4.22 | 41 | 5.97 |
| 2 | 35 | 3.62 | 41 | 4.26 | 40 | 5.63 |
| 3 | 32 | 3.82 | 36 | 3.70 | 37 | 5.36 |
| 4 | 29 | 4.23 | 29 | 4.25 | 34 | 6.51 |
| 5 | 27 | 3.59 | 26 | 4.11 | 26 | 5.05 |
| 6 | 26 | 4.36 | 24 | 3.54 | 22 | 5.29 |
| 7 | 19 | 3.06 | 21 | 3.52 | 18 | 5.04 |
| 8 | 16 | 3.09 | 19 | 2.96 | 15 | 4.50 |
| 9 | 14 | 2.50 | 17 | 2.94 | 13 | 4.65 |
| 10 | 12 | 2.87 | 14 | 2.92 | 11 | 3.67 |
| Weighted Average | | 3.68 | | 3.80 | | 5.43 |

The average maintenance doses (mg/kg) were calculated from the interval between doses and the dose rate for the first five maintenance doses of propofol. Averages were 2.20 mg/kg for Group 1 (range 1.52-3.06 mg/kg), 1.63 mg/kg for Group 2 (range 1.48-1.98 gm/kg) and 1.81 mg/kg for Groups 8, 9 and 10 (range 1.74-1.85 mg/kg), representing a sparing of 35% with Ace and 21% for premedicant combinations (Groups 8, 9 and 10). The higher dose used in Groups 8, 9 and 10 may account for the longer time interval between injections shown above.

Maintenance with Gas Inhalants: The mean duration of anesthesia in Groups 3, 4, 5, 6 and 7 was, respectively, 87.5, 145.4, 113.8, 162.8, 113.5 and 135.3 min. The number of cases requiring supplemental doses to complete the transition to gas inhalant was 40 for Groups 3-7. Supplemental doses were similar to those used for maintenance anesthesia with propofol.

Additional dose(s) of propofol were administered to deepen anesthesia in 44 cases in Groups 3-7. Supplemental doses were similar to those used for maintenance anesthesia with propofol.

Vaporizer settings for each of Groups 3 through 6 (isoflurane) and 7 (halothane) are presented in the table below. The initial vaporizer setting for isoflurane was highest in Group 3 (no preanesthetic) and lower in each of the groups administered preanesthetics. At 30 min of inhalant anesthetic, the vaporizer setting was lower in each of the groups compared to the initial setting, indicating a stabilization of the depth of anesthesia. Vaporizor settings were typical for isoflurane anesthesia, however, initial halothane settings were higher than the 1.5-2.0% typically recommended for maintenance (Muir *et al*., 1995). Vaporizer settings changed minimally between 30 and 60 min of the procedure in any of the groups.

Average Vaporizer Settings during Maintenance (all sites)

| *Group* | *Preanesthetic* | *N* | *First* | *10 min* | *30 min* | *60 min* |
|---|---|---|---|---|---|---|
| 3 | None/Iso | 52 | 2.51 | 2.52 | 2.24 | 2.24 |
| 4 | Ace + Oxy/Iso | 54 | 2.25 | 2.15 | 1.98 | 1.91 |
| 5 | Xyl + But/Iso | 46 | 2.40 | 2.03 | 2.03 | 2.07 |
| 5A | Diaz + Oxy/Iso | 13 | 1.92 | 2.04 | 1.72 | 2.18 |
| 6 | Diaz + But/Iso | 53 | 2.30 | 2.27 | 2.12 | 2.09 |
| 7 | Ace + Oxy/Hal | 56 | 2.37 | 2.19 | 1.83 | 1.72 |

**Anesthesia**

Induction: The quality of induction was judged by the investigator; results are provided in the following table. Induction was judged as Excellent or Good in 396 of 419 cases (94%). Most of the inductions judged Fair or Poor involved animals in which additional doses of propofol were required for intubation.

| *Treatment Group* | *Treatment* | *Quality of Induction* | | | | *Total* |
|---|---|---|---|---|---|---|
| | | *Excellent* | *Good* | *Fair* | *Poor* | |
| | | *N* | *N* | *N* | *N* | *N* |
| 1 | None | 35 | 8 | 5 | 1 | 49 |
| 2 | Ace | 30 | 16 | 1 | 1 | 48 |
| 3 | None/Iso | 27 | 19 | 5 | 1 | 52 |
| 4 | Ace + Oxy/Iso | 46 | 8 | 0 | 0 | 54 |
| 5 | Xyl + But/Iso | 35 | 10 | 1 | 0 | 46 |
| 5A | Diaz + Oxy/Iso | 9 | 4 | 0 | 0 | 13 |
| 6 | Diaz + But/Iso | 33 | 16 | 4 | 0 | 53 |
| 7 | Ace + Oxy/Hal | 46 | 9 | 1 | 0 | 56 |
| 8 | Ace + Oxy/Prop | 12 | 2 | 2 | 0 | 16 |
| 9 | Xyl + But/Prop | 16 | 0 | 0 | 0 | 16 |
| 10 | Diaz + But/Prop | 14 | 1 | 1 | 0 | 16 |
| Total | | 303 | 93 | 20 | 3 | 419 |

Maintenance: The assessment of maintenance by the investigator is provided in the following table. Maintenance was judged as Good to Excellent in 118 of 145 (81%) of the cases maintained with propofol (Groups 1, 2, 8, 9 and 10). The assessments of maintenance with inhalant following propofol induction (Groups 3-7) were Good or Excellent in 243 of 274 (89%) cases.

| *Treatment Group* | *Treatment* | *Quality of Maintenance* *Excellent* *N* | *Good* *N* | *Fair* *N* | *Poor* *N* | *N/A** *N* | *Total* *N* |
|---|---|---|---|---|---|---|---|
| 1 | None | 22 | 18 | 7 | 0 | 2 | 49 |
| 2 | Ace | 23 | 13 | 8 | 2 | 2 | 48 |
| 3 | None/Iso | 16 | 24 | 12 | 0 | 0 | 52 |
| 4 | Ace + Oxy/Iso | 28 | 25 | 1 | 0 | 0 | 54 |
| 5 | Xyl + But/Iso | 24 | 16 | 5 | 1 | 0 | 46 |
| 5A | Diaz + Oxy/Iso | 4 | 8 | 1 | 0 | 0 | 13 |
| 6 | Diaz + But/Iso | 21 | 25 | 7 | 0 | 0 | 53 |
| 7 | Ace + Oxy/Hal | 24 | 28 | 4 | 0 | 0 | 56 |
| 8 | Ace + Oxy/Prop | 8 | 8 | 0 | 0 | 0 | 16 |
| 9 | Xyl + But/Prop | 8 | 7 | 1 | 0 | 0 | 16 |
| 10 | Diaz + But/Prop | 5 | 6 | 2 | 1 | 2 | 16 |
| Total | | 183 | 178 | 48 | 4 | 6 | 419 |

* not available

Recovery: Time to recovery events are provided in the following table and support the rapid termination of anesthetic effect of propofol. For animals maintained on propofol (Groups 1, 2, 8, 9 and 10), recoveries were generally similar among unpremedicated and premedicated animals. For animals maintained on gas inhalants (Groups 3-7), recovery events were prolonged in dogs maintained with either isoflurane or halothane following premedication with Ace + Oxy (Groups 4 and 7). Otherwise, recovery times were similar among premedicated and unpremedicated groups.

Recovery was Excellent or Good in 134 of 145 (92%) of the cases in which animals were maintained on propofol (Groups 1, 2, 8, 9 and 10). The assessments of recovery from inhalant anesthesia following propofol induction were Good or Excellent in 255 of 274 (93%) cases (Groups 3-7).

| *Treatment Group* | *Treatment* | *Time to Extubation min Mean (Range)* | *Time to Sternal Recumbency min Mean (Range)* | *Quality of Recovery* | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | *Excel N* | *Good N* | *Fair N* | *Poor N* | *N/A* N* | *Total N* |
| 1 | None | 11.5 (1-36) | 17.0 (4-60) | 34 | 10 | 5 | 0 | 0 | 49 |
| 2 | Ace | 9.8 (-2-18) | 15.1 (6-32) | 41 | 5 | 0 | 1 | 1 | 48 |
| 3 | None/Iso | 11.3 (0-103) | 15.7 (0-104) | 38 | 11 | 2 | 1 | 0 | 52 |
| 4 | Ace + Oxy/Iso | 22.4 (2-141) | 32.7 (2-148) | 35 | 13 | 6 | 0 | 0 | 54 |
| 5 | Xyl + But/Iso | 10.2 (0-42) | 19.5 (0-85) | 33 | 10 | 2 | 1 | 0 | 46 |
| 5A | Diaz + Oxy/Iso | 11.7 (1-48) | 18.9 (4-48) | 8 | 5 | 0 | 0 | 0 | 13 |
| 6 | Diaz + But/Iso | 9.9 (1-33) | 15.9 (2-55) | 34 | 14 | 5 | 0 | 0 | 53 |
| 7 | Ace + Oxy/Hal | 25.0 (3-90) | 42.2 (3-157) | 25 | 29 | 2 | 0 | 0 | 56 |
| 8 | Ace + Oxy/Prop | 11.2 (2-24) | 17.3 (7-40) | 16 | 0 | 0 | 0 | 0 | 16 |
| 9 | Xyl + But/Prop | 12.3 (3-27) | 17.3 (3-35) | 15 | 0 | 0 | 1 | 0 | 16 |
| 10 | Diaz +But/Prop | 9.9 (0-19) | 17.1 (7-39) | 11 | 2 | 0 | 0 | 3 | 16 |
| Total | | | | 290 | 99 | 22 | 4 | 4 | 419 |

* not available

**Physiological Effects:**
Mean values for heart rate (pulse), respiration rate and mean arterial blood pressure are provided in the table below, as measured prior to premedication, prior to induction (after premedication) and 5 minutes after induction. Propofol had minimal effect on pulse but a marked effect on respiration rate. Propofol induction also produced a decrease in blood pressure, however, resultant pressures were generally clinically acceptable.

| *Treatment Group* | *Treatment* | *Pulse bpm (mean [N])* | | | *Respiration Rate per min (mean [N])* | | | *Mean Blood Pressure mmHg (mean [N])* | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | *Before Premed* | *Before Induct* | *5 Min After Induct* | *Before Premed* | *Before Induct* | *5 Min After Induct* | *Before Premed* | *Before Induct* | *5 Min After Induct* |
| 1 | None | - | 114 (48) | 120 (48) | - | 49 (30) | 33 (48) | - | 101(29) | 96 (46) |
| 2 | Ace | 112 (48) | 107 (47) | 102 (47) | 54 (23) | 39 (29) | 26 (46) | 96 (28) | 112 (29) | 89 (46) |
| 3 | None/Iso | - | 110 (51) | 112 (52) | - | 47 (36) | 30 (48) | - | 108 (24) | 84 (50) |
| 4 | Ace + Oxy/Iso | 106 (53) | 95 (54) | 94 (50) | 43 (34) | 43 (41) | 19 (49) | 99 (12) | 92 (13) | 69 (49) |
| 5 | Xyl + But/Iso | 114 (46) | 85 (44) | 94 (43) | 44 (29) | 24 (39) | 11 (43) | 104 (9) | 82 (11) | 91 (39) |
| 5A | Diaz + Oxy/Iso | 92 (14) | 90 (14) | 87 (13) | 30 (4) | 30 (3) | 24 (13) | 104 (8) | 92 (7) | 69 (13) |
| 6 | Diaz + But/Iso | 112 (53) | 108 (52) | 106 (51) | 41 (35) | 38 (40) | 23 (47) | 99 (13) | 97 (13) | 76 (51) |
| 7 | Ace + Oxy/Hal | 110 (55) | 96 (56) | 88 (56) | 41 (32) | 46 (42) | 24 (50) | 102 (15) | 93 (18) | 70 (54) |
| 8 | Ace + Oxy/Prop | 115 (16) | 92 (15) | 94 (16) | 51 (9) | 31 (9) | 41 (14) | 108 (14) | 92 (16) | 73 (16) |
| 9 | Xyl/But/Prop | 123 (13) | 86 (15) | 94 (16) | 31 (9) | 21 (12) | 24 (16) | 108 (10) | 100 (14) | 92 (14) |
| 10 | Diaz/But/Prop | 118 (15) | 110 (16) | 111 (16) | 41 (11) | 30 (7) | 22 (16) | 99 (13) | 89 (14) | 83 (15) |

Side Effects
Side effects in this study are listed below, by organ system:

Respiratory
Apnea (n=110)
Tachypnea (n=180)
Labored Breathing (n=3)

Cardiovascular
Hypotension (n=98)
Membrane Cyanosis (n=14)
Bradycardia (n=72)
Tachycardia (n=45)
Arrhythmias (n=18)

Central Nervous System
Excitation (n=31)
Excessive Depression (n=2)

Muscular
Fasciculations (n=68)
Muscle Tenseness (n=18)
Paddling (n=12)

Gastrointestinal
Emesis (n=8)
Retching (n=3)
Salivation (n=18)

Respiratory effects:

Respiratory effects were the most commonly observed side effects with propofol. Tachypnea occurred in a total of 180 dogs: during preinduction only in 45 patients, during maintenance only in 44 patients, and in both preinduction and maintenance in 91 patients. Tachypnea was the most common side effect observed during the time interval from the injection of the preanesthetic to induction of anesthesia with propofol. Apnea occurred in 110 patients: 39 patients during propofol maintenance and 71 during inhalant maintenance. Apnea occurred most often during the interval immediately following induction with propofol (0 to 5 min postintubation). Incidences of apnea varied in duration from a few seconds to several minutes. All instances of apnea in this investigation were clinically manageable and no adverse effects were observed.

Cardiac Arrhythmias:

Of the 15 cardiac arrhythmias that were observed, 2 dogs developed ventricular premature contractions (VPCs) following administration of maintenance doses of propofol. Additionally, transient PVCs were observed in 3 dogs after 40 min of inhalational anesthesia, one of which was attributable to direct myocardial irritation. The remaining arrhythmias observed (premature junctional complexes, second degree AV block, respiratory sinus arrhythmia) were not considered to be related to propofol administration.

| **Arrhythmia** | **Propofol induction/ Inhalant maintenance** | **Propofol induction/ Propofol maintenance** |
|---|---|---|
| VPC | 3 (#MO22, MO46, WI65)<br>1 with myocardial irritation<br>2 at >40 min inhalational anesthesia | 2 (#MO33, MO56)<br>isolated, transient |
| Premature junctional complex | 1 (#WI9) at 20-140 min | - |
| Second degree AV block | 3 (#WI4, WI48, WI49)<br>1 at >50 min inhalational anesthesia<br>2 after glycopyrrolate | - |
| Respiratory sinus arrhythmia | 3 (WI1, WI56, WI86)<br>at 50-80 min | - |

Supplemental Oxygen

Due to internal facility procedures, most of the patients at TX and WI received supplemental $O_2$ during propofol maintenance, whereas fewer than half the patients received supplemental $O_2$ at OH and MO. A total of 66 of 145 dogs (46%) maintained with bolus doses of propofol were not given supplemental oxygen. Of these, five received supplemental oxygen later in the anesthesia, two of which were based on low hemoglobin oxygen saturation. Thus, although a large number of dogs in this study were maintained on propofol in the absence of supplemental oxygen, it is important to have equipment available for supplemental ventilation of the patient, if required, based on the respiratory depressant effect of propofol.

Sighthounds

A total of 27 Sighthounds (25 Greyhounds and one each Italian Greyhound and Scottish Deerhound) were enrolled in the study. Key results are shown in the following table. Mean induction dose and time to intubation was similar between Sighthounds and non-Sighthounds. Time to extubation and sternal recumbency were longer in Sighthounds than other animals, both in the presence and absence of premedicants.

| *Group* | *Premedicant(s)* | *Mean Induction Dose (mg/kg)* | *Mean Time to Intubation (min)* | *Time to Extubation (min)* | *Mean Time to Sternal Recumbency (min)* |
|---|---|---|---|---|---|
| 1 + 3 | None | 4.7 | 2.2 | 11.3 | 24.9 |
| 4-10 | All others | 3.1 | 1.7 | 18.3 | 34.8 |

Compromised Animals
Twenty-two (22) animals enrolled in this study were considered compromised by the investigator. Underlying diseases in these animals varied; as such, insufficient data are available on the effect of propofol anesthesia on animals of specific disease states.

**6. Safety**

The safety of propofol was demonstrated in two (2) pivotal studies:

**a. Tolerance Study**
**b. Target Animal Safety Study**

**a. TOLERANCE STUDY**

**STUDY PERSONNEL**
**Sponsor Monitor:**
Riemond H. Rippel, PhD
Animal Health Products
Abbott Laboratories
1401 N. Sheridan Road
North Chicago, IL 60064-4000

**Study Investigator:**
William W. Muir III, DVM, PhD
Dept. Veterinary Clinical Sciences
Ohio State University
Columbus, OH 43210-1089

**STUDY DATES:** May 24 -December 2, 1996

**STUDY OBJECTIVES**
This study was conducted to evaluate the tolerance of young-adult non-premedicated Beagle dogs to various doses of propofol.

**STUDY DESIGN**
Following an initial dose of 6.5 mg/kg propofol to each dog, the dose of propofol was incrementally increased by 2.5 mg/kg until a Serious Adverse Effect was seen in each animal. This defined the toxic dose. One additional dose, equivalent to 2.5 mg greater than the toxic dose (excessive dose), was then administered to each dog. Each administration of propofol was followed by a 4 to 5 d wash-out period.

**MATERIALS AND METHODS**
**Animals**
Number: 2 males and 2 females
Breed: Beagle
Age: 8-12 months
Weight: 8.8-11.3 kg
Sex: males and females

**Anesthetic Procedure**
Propofol administration:
Propofol was administered at the rate of 20 mg (2 mL) over approximately 10 s as a single intravenous bolus injection.

**Variables Measured or Observed**
Propofol Dose: Dose producing a serious adverse effect, defined as: apnea of $\geq$ 90 s; heart rate of $\leq$50 beats/min; mean arterial blood pressure of $\leq$ 60 mm Hg; potentially lethal ECG rhythm or adverse clinical signs (e.g. convulsions) during anesthesia.
Anesthesia: Recovery times
Physiological: Mucous membrane color, rectal temperature, respiration rate, systolic and diastolic arterial pressure were measured during each anesthetic treatment. Respiration rate, heart rate, clinical observations (including incidence and duration of apnea), and body weight were assessed once daily throughout the study.

**RESULTS**

**Propofol Dose:** Apnea was the Serious Adverse Effect which defined the toxic dose for each dog. A dose of 16.5 mg/kg for one dog, 19.0 mg/kg for two dogs and 21.5 mg/kg for one dog produced apnea of $\geq$ 90 s duration.

**Anesthesia:** Propofol produced excellent short-term anesthesia as suggested by smooth, quiet and uneventful induction, maintenance and recovery. Pain on injection was not observed at the doses or rate of administration used in this study. Time to return of the swallow reflex, sternal recumbency and standing recovery increased as the dose of propofol was increased, as seen in the following table.

| *Dose (mg/kg)* | *N* | *Mean Duration Apnea (s)* | *Mean Time to (min)* | | | |
|---|---|---|---|---|---|---|
| | | | *Intubation* | *Swallow* | *Sternal* | *Standing* |
| *6.5* | *4* | *10* | *2* | *8* | *8* | *13* |
| 9.0 | 4 | 48 | 2 | 16 | 18 | 21 |
| 11.5 | 4 | 45 | 2 | 21 | 26 | 27 |
| 14.0 | 4 | 38 | 2 | 21 | 24 | 28 |
| 16.5 | 4 | 74 | 2 | 25 | 31 | 34 |
| 19.0 | 4 | 108 | 2 | 31 | 37 | 40 |
| 21.5 | 3 | 120 | 2 | 30 | 37 | 40 |
| 24.0 | 1 | 95 | 2 | 37 | 49 | 49 |

**Physiological Effects:**

The duration of apnea tended to increase in a dose-related manner at doses greater than 14 mg/kg body weight. The mean duration of apnea at the toxic dose was 111 ± 15 s and 120 ± 17 s at the excessive dose. In all instances, dogs either began spontaneous respiration voluntarily or were successfully ventilated with 1 to 2 breaths/min; oxygen supplementation was not used. Increasing the dose of propofol produced greater decreases in respiration rate and a slower return to preanesthesia rates. Apnea and hypoventilation at higher doses were associated with changes in mucous membrane color (cyanosis).

Propofol effected dose-related increases in heart rate, which peaked at approximately 1 to 4 min of anesthesia and then declined to a rate slightly below baseline by 20 min of anesthesia. At doses of 14 mg/kg or less, changes in arterial blood pressure were characterized by an initial increase, followed by a decrease in late anesthesia. Doses equal to or greater than 16.5 mg/kg produced a gradual decrease in arterial pressure throughout the anesthetic period, although pressure was always within acceptable limits.

Propofol did not produce meaningful changes in the ECG or body temperature at any dose studied. Slight to moderate muscle twitching was observed during 8 of the 30 separate anesthetic episodes in this study, usually during the lighter stages of anesthesia.

Heart rate and respiration rate, measured daily, were normal for the duration of the study. No untoward clinical observations or body weight changes were observed.

**DISCUSSION/COMMENTS**
These data indicate that propofol is well tolerated by the dog and that the mean toxic dose of 19.0 mg/kg is approximately 3.5 times the average dose required to produce acceptable anesthesia in the non-premedicated dog (5.5 mg/kg). Also, a single mean bolus dose of 16.5 mg/kg propofol was tolerated without a Serious Adverse Effect.

**b. TARGET ANIMAL SAFETY**

**STUDY PERSONNEL**
**Sponsor Monitor:**
Riemond H. Rippel, PhD
Animal Health Products
Abbott Laboratories
1401 N. Sheridan Road
North Chicago, IL 60064-4000

**Study Investigator:**
William W. Muir III, DVM, PhD
Dept. Veterinary Clinical Sciences
Ohio State University
Columbus, OH 43210-1089

**STUDY DATES:** October 28-December 27, 1996

**STUDY OBJECTIVES:**
The purpose of the study was to assess the safety of propofol in dogs under exaggerated conditions of use, and to document the signs and effects, if any, associated with the use of propofol in dogs.

**STUDY DESIGN**
Three groups of dogs were evaluated. Two propofol groups received total doses of either 11.6 (Low Dose) or 29.7 mg/kg (High Dose) at each episode. Anesthesia was induced with doses of propofol of 6.5 or 19.5 mg/kg and maintained with three and six bolus injections of 1.7 mg/kg propofol, respectively. A third group of dogs was injected with saline (Controls) at a volume equal to that administered to the High Dose dogs. Each group included a total of 8 dogs (4 males and 4 females). Dogs were anesthetized every other day over an 11-d period (six anesthetic episodes for each dog).

## MATERIALS AND METHODS

### Animals

Number: 12 males and 12 females
Breed: Beagle
Age: 5.0-5.5 months
Weight: 5.0-8.2 kg
Sex: males and females

### Anesthetic Procedure

Propofol administration: Propofol was administered at the rate of 20 mg (2 mL) over approximately 10 s as a single intravenous bolus injection.

### Variables Measured or Observed

Anesthesia: Recovery times
Physiological: Clinical observations were made twice daily beginning on d -14; heart rate, respiration rate, body temperature and lung auscultation were evaluated daily beginning on d -7. Body weight was measured weekly during acclimation and on the day after each anesthetic episode. Food consumption was measured on d -5, -3, -1 and daily during the treatment period (d 0-13). Physiologic responses were measured before and at specified times during each anesthetic episode. All dogs were necropsied on d 13 of the study.

## RESULTS

**Anesthesia:** Although the interval between maintenance doses of propofol was only slightly longer for the High Dose group compared to the Low Dose group, indices of recovery were more prolonged with the High Dose dogs, except after the first episode of anesthesia in which there was a small difference between the doses. The time to recovery events increased after the first anesthetic episode, but did not increase markedly beyond that point.

Mean Time (min) From Last Maintenance Dose to Recovery Events

| *Treatment Group* | *Recovery Event* | *Episode* 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|---|
| Low | Swallow | 6 | 7 | 10 | 9 | 11 | 11 |
| | Standing | 9 | 12 | 14 | 12 | 14 | 14 |
| High | Swallow | 10 | 10 | 13 | 13 | 13 | 14 |
| | Standing | 14 | 22 | 24 | 24 | 25 | 26 |

### Physiological Effects:

Propofol did not adversely affect body weight, food consumption, daily respiration rate, temperature or daily clinical observations. Average daily heart rate tended to increase over time in dogs that received propofol, but was within the normal range for Beagles.

During anesthesia at the Low Dose of propofol, transient increases in respiratory rate occurred at 1 min after induction and declined to baseline within 5 minutes. Respiratory rate declined initially in response to the High Dose of propofol, then returned to or above baseline within 10 minutes. Heart rate increased after induction in both dose groups and gradually returned to baseline. Transient, clinically acceptable increases in systolic and mean blood pressure and decreases in diastolic blood pressure (High Dose only), occurred immediately (1 min) after propofol administration in both groups.

The duration of apnea averaged 28 and 70 s after induction doses of 6.5 and 19.5 mg/kg, respectively, and did not increase with repeated episodes of propofol administration. This supports the observation that there is an absence of cumulative effects of propofol when administered repeatedly. All animals which became apneic resumed breathing spontaneously; at no time in the study was oxygen supplementation or assisted ventilation required.

Tachypnea, another common side effect, was transient and clinically manageable; its incidence was similar among the Low and High Dose groups. Muscle fasciculations which were observed during maintenance with intermittent bolus injections were considered related to a light stage of anesthesia. Changes in mucous membrane color were consistent with mild respiratory depression and subsequent vasodilation. Mucous membrane color was normal in all dogs within 5 min of induction.

Hematology and clinical chemistry findings were incidental and not attributed to the administration of propofol. No differences in organ weights or organ weight ratios were observed.

**DISCUSSION/COMMENTS**
The results of this Target Animal Safety Study indicate that propofol at a total dose of 29.7 mg/kg body weight produced no toxicological effects upon repeated administration in the dog. This study supports the safe use of propofol for the induction of anesthesia in dogs and for the maintenance of anesthesia for procedures of short duration.

**7. Supportive Studies**

a. Pharmacokinetics and Metabolism

1. Cockshott *et al*. (1992)
The pharmacokinetics of propofol was studied in three dogs after a single bolus injection of 7 mg/kg or after a single bolus (7 mg/kg) injection followed by infusion at 28 mg/kg/hour for 6 hours. Blood samples were collected from the saphenous vein over a 12-hour period. In a separate study, 16 dogs were treated with a single bolus (7.5 mg/kg) injection following by infusion at 30 mg/kg/hour for 4 hours of each of four occasions over a 2-week period. Blood samples were collected from the saphenous vein during the recovery period. Plasma protein binding was determined using *in vitro* techniques.

The pharmacokinetics of propofol was described in the dog as a three compartment open mammilary model. Half-lives for the alpha, beta and gamma elimination phases were 2.2, 31 and 303 minutes, respectively, following bolus dosing, and 7.4, 53 and 725 minutes following infusion at 28 mg/kg/hour. Clearance in the infusion study was approximately half that of the bolus dose study. Plasma protein binding was determined to be 98.1% in the dog.

2. Nolan *et al*. (1993)
The pharmacokinetics of propofol administered as a bolus dose (6.5 mg/kg) by intravenous injection was studied in six dogs. The effect of halothane or nitrous oxide maintenance on propofol pharmacokinetics was also studied in six dogs undergoing routine anesthesia. The pharmacokinetics of propofol was described as bi-exponential in some dogs and tri-exponential in others. The terminal elimination half-life was 75 to 91 minutes. Propofol exhibited a large volume of distribution at steady state (4863 to 4889 mL/kg) and rapid clearance (56 to 58 mL/kg/min). There were no significant differences in the pharmacokinetics of propofol based on inhalant maintenance.

3. Simons *et al*. (1991)
The pharmacokinetics of $^{14}$C-propofol was studied in dogs. Bolus intravenous doses (7.2 mg/kg) or intravenous infusion doses (7.3 mg/kg followed by 0.47 mg/kg/minute for 6 hours) were followed by sampling via the saphenous vein over a period of 24 hours and the collection of excreta over 4 days. Propofol was eliminated primarily in the urine, with a lower amount of fecal elimination. Maximum concentrations of radioactivity were observed in the blood 2 to15 minutes after bolus administration. Propofol concentrations were highest at 2 minutes, followed by a rapid decline. The pharmacokinetics were best described by a tri-exponential equation.

Propofol was extensively metabolized to glucuronide or sulphate conjugates. No unchanged propofol was excreted into the urine.

b. Relationship of Rate of Injection to Incidence of Apnea

Smith *et al.* (1993)
Forty (40) dogs requiring general anesthesia were included in this study. Dogs were divided into four groups and treated with propofol alone (6 mg/kg IV), propofol with acepromazine (0.1 mg/kg IM), propofol with diazepam (0.2 mg/kg IV) or propofol with acepromazine (0.02 mg/kg IM) and butorphanol (0.04 mg/kg, IM). Dogs were then maintained on 1-3% isoflurane. Heart rate, systolic arterial blood pressure, blood gases and pH, respiration rate, quality of recovery, and adverse effects were recorded.

A total of 34 of 40 dogs treated with propofol became apneic during the experiment. According to the authors, the effect of propofol on respiration is similar to that of thiopental. The authors noted that the rapid delivery of the dose (over 5 seconds) may have contributed to the respiratory depression. Venous $P_{CO2}$ increased and pH decreased immediately after propofol administration and was associated with the respiratory

depression. Significant decreases in systemic arterial pressure from baseline to 5 minutes after induction were observed in animals treated with acepromazine or acepromazine/butorphanol.

Cyanosis was observed in 2 of 40 cases, and pain on injection in 3 of 40 cases. Several other animals exhibited salivation, retching or vomiting. One dog in this study exhibited premature ventricular depolarization. Excitement was observed in 1 of 40 unpremedicated animals and 3 of 40 animals treated with diazepam.

c. Arrhythmogenicity

Kamibayashi *et al*., 1991
The arrhythmogenic threshold of epinephrine was determined during anesthesia with propofol alone and in the presence of etomidate, and compared to that during anesthesia produced by halothane (1.3 MAC) or etomidate (2 mg/kg followed by maintenance at 8 mg/kg/hour). During propofol anesthesia (10 mg/kg followed by maintenance at 40 mg/kg/hour), the arrhythmogenic plasma concentration of epinephrine was 27 ng/mL; this was similar to that for halothane and lower than that for etomidate. In the presence of etomidate, propofol reduced the arrhythmogenic plasma concentration of epinephrine in a dose-dependent manner. Infusion of propofol to etomidate-anesthetized dogs at rates of 5, 10 and 20 mg/kg/hour resulted in arrhythmogenic plasma concentrations of epinephrine of 183, 89 and 27 ng/mL, respectively.

**8. Human User Safety**
Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. The drug is labeled for use in dogs which are non-food animals.

Labeling contains adequate warnings against accidental self-administration and the risk of drug diversion. An "800" number is provided by the sponsor for the provision of Material Safety Data Sheets (MSDS).

**9. Agency Conclusions**
The data in support of this NADA comply with the requirements of Section 512 of the Act and Section 514 of the implementing regulations, and demonstrate that Propoflo™, when used under labeled conditions of use, is safe and effective.

Under Section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval for non-food producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval. The application contains substantial evidence of the effectiveness of the drug involved and studies of animal safety required for the approval of the application and conducted or sponsored by the applicant.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is required to administer general anesthesia in dogs.

**10. References**

Cockshott, I.D., E.J. Douglas, G.F. Plummer, and P.J. Simons. The pharmacokinetics of propofol in laboratory animals. *Xenobiotica* 22(3): 369-375 (1992).

Geel, J.K., The effect of premedication on the induction dose of propofol in dogs and cats. *Tydskr. S. Afr. Vet. Assoc.* 32(3): 118-123 (1991).

Hall, L.W., and J.P. Chambers. A clinical trial of propofol infusion anaesthesia in dogs. *J. Small Animal Practice* 28: 623-637 (1987).

Kamibayashi, T., Y. Hayashi, K. Sumikawa, A. Yamatodani, K. Kawabata, and I. Yoshiya. Enhancement by propofol of epinephrine-induced arrhythmias in dogs. *Anesthesiol.* 75: 1035-1040 (1991).

Morgan, D.W.T. and K. Legge. Clinical evaluation of propofol as an intravenous anaesthetic agent in cats and dogs. *Vet. Record* 124: 31-33 (1989).

Muir, W.W., J.A.E. Hubbell, R.T Skarda, and R.M. Bednarski. *Handbook of Veterinary Medicine,* Second Edition. Mosby-Year Book, Inc. (1995).

Nolan, A.M., J. Reid, and S. Grant. The effects of halothane and nitrous oxide on the pharmacokinetics of propofol in dogs. *J. Vet. Pharmacol. Therap.* 16: 335-342 (1993).

Plumb, D.C. ed. *Veterinary Drug Handbook*, Second Edition. Iowa State University Press, Ames, IA (1995).

Robertson, S.A., S. Johnston, and J. Beemsterboer. Cardiopulmonary, anesthetic, and postanesthetic effects of intravenous infusions of propofol in Greyhounds and non-Greyhounds. *Am. J. Vet. Res.* 53(6): 1027-1032 (1992).

Simons, P.J., I.D. Cockshott, E.J. Douglas, E.A. Gordon, S. Knott, and R.J. Ruane. Species differences in blood profiles, metabolism and excretion of $^{14}$C-propofol after intravenous dosing to rat, dog and rabbit. *Xenobiotica* 21(10): 1243-1256 (1991).

Smith, J.A., J.S. Gaynor, R.M. Bednarski and W.W. Muir. Adverse effects of administration of propofol with various preanesthetic regimens in dogs. *JAVMA*. 202:1111-1115 (1993).

Watkins, S.B., L.W. Hall, and K.W. Clarke. Propofol as an intravenous anesthetic agent in dogs. *Vet Rec.* 120: 326-329 (1987).

Watney, G.C.C. and L.S. Pablo. Median effective dosage of propofol for induction of anesthesia in dogs. *Am. J. Vet. Res.* 53(12): 2320-2322 (1992).

Weaver, B.M.Q. and D. Raptopoulos. Induction of anaesthesia in dogs and cats with propofol. *Vet. Record* 126: 617-620 (1990).

Zoran, D.I., D.H. Riedesel, and D.C. Dyer. Pharmacokinetics of propofol in mixed-breed dogs and Greyhounds. *Am. J. Vet. Res.* 54 (5): 755-760 (1993).

**11. Labeling** (attached)

Package Insert

Vial Label

Carton Label