FREEDOM OF INFORMATION SUMMARY

1. General Information:

A.	NADA Number:	141-070
B.	Sponsor:	Mallinckrodt Veterinary, Inc. 421 East Hawley Street Mundelein, IL 60060
C.	Generic Name:	Propofol
D.	Trade Name:	RAPINOVET®
E.	Marketing Status:	Rx

2. Indications for Use:

RAPINOVET is an anesthetic injection for use in dogs as follows:

a) As a single injection to provide general anesthesia for procedures lasting up to five minutes.

b) For induction and maintenance of general anesthesia using incremental doses to effect.

c) For induction of general anesthesia where maintenance is provided by inhalant anesthetics.

Propofol is an effective anesthetic when used in accordance with good veterinary anesthetic practices. Propofol properties include smooth induction and rapid recovery. Propofol may be used alone to induce a relatively short period of anesthesia. Propofol may also maintain anesthesia for longer periods, through intermittent injections. Both induction and maintenance may be preceded by a pre-anesthetic drug(s). Finally, propofol may be used to induce anesthesia that will be maintained with an inhalant anesthetic.

Induction of anesthesia will usually be observed within 30-60 seconds after the end of administration (administration should take 60-90 seconds). The duration of anesthesia following the recommended induction dose (5.5 - 7.0 mg/kg without premedication) is generally 5 - 7 minutes. The duration of anesthesia following maintenance doses varies depending upon the dose; generally 2 - 6 minutes after 1.1 mg/kg and 6 - 10 minutes after 3.3 mg/kg. RAPINOVET is particularly suitable for cases where a rapid recovery is required. Full standing recovery is generally observed within 10 - 20 minutes after the end of anesthesia, regardless of the duration of anesthesia. Recovery may be delayed in sighthounds or if pre-anesthetics are administered.

3. Dosage Form, Route of Administration, and Recommended Dosages:

RAPINOVET is an oil in water emulsion containing 10 mg of propofol per mL. It is available in a 20 mL sealed ampule, and is intended for intravenous use only.

a. INDUCTION OF GENERAL ANESTHESIA:

For induction, RAPINOVET injection should be titrated against the response of the patient over approximately 60 - 90 seconds or until clinical signs show the onset of anesthesia.

The average induction dose ranges and dosage rates for healthy dogs given propofol alone, or when propofol is preceded by premedicants, are indicated in the following table (the table is for guidance only; in practice, the dose should be based upon patient response):

Induction Dosage Guidelines

	Propofol Induction Dose		Propofol Rate of Administration		
Preanesthetic	mg/kg	mg/lb	seconds	mg/kg/min	mL/kg/min
None	5.5-7.0	2.5-3.2	60-90	3.7-7.0	0.37-0.70
Acepromazine	4.0-4.4	1.8-2.0	60-90	2.7-4.4	0.27-0.44
Xylazine	2.2-3.3	1.0-1.5	60-90	1.5-3.3	0.15-0.33
Oxymorphone	2.2-3.3	1.0-1.5	60-90	1.5-3.3	0.15-0.33
Medetomidine	2.2-2.8	1.0-1.3	60-90	1.5-2.8	0.15-0.28
Butorphanol	4.4-5.0	2.0-2.3	60-90	2.9-5.0	0.29-0.50
Acepromazine /Butorphanol	2.2-2.8	1.0-1.3	60-90	1.5-2.8	0.15-0.28

The recommended dosages of tranquilizers, sedatives, or analgesics administered as preanesthetic medications (listed below) may be lower than the label directions for use as a single medication (see references: Thurmon et al., 1996, Mallinckrodt clinical studies).

Acepromazine	0.03 - 0.1 mg/kg	IM, SC, IV
Xylazine	0.25 - 0.5 mg/kg	IV
	0.5 - 1.0 mg/kg	IM, SC
Oxymorphone	0.1 - 0.2 mg/kg	IM, SC, IV
Medetomidine*	10 – 40 μg/kg	IM, IV
Butorphanol*	0.1-0.3 mg/kg	IM, SQ

*Medetomidine and butorphanol are not approved for preanesthesia in dogs; only information concerning approved canine preanesthetics is included on product labeling. However, the potential for the extralabel use of these two drugs as preanesthetics warranted their inclusion in pivotal efficacy studies and a complete discussion of all study results is included in this FOI Summary.

The preanesthetic use of the drugs listed above markedly reduces propofol requirements. As with other sedative hypnotic agents, the amount of opioid, α-2 agonist, and/or benzo-diazepine premedication will influence the response of the patient to an induction dose of RAPINOVET. The induction dose will also be influenced by the interval between the administration of premedication and induction and the rate of administration of propofol.

If RAPINOVET is injected too slowly (> 90 seconds), an inadequate plane of anesthesia may be achieved. If this occurs, an additional low dose of propofol may be administered (1.1 mg/kg) to facilitate intubation or the transition to inhalant maintenance anesthesia.

b. MAINTENANCE OF GENERAL ANESTHESIA:

1) Intermittent Propofol Injections:

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

	Propofol Maintenance Dose		Propofol Rate of Administration		
Preanesthetic	mg/kg	mg/lb	seconds	mg/kg/min	mL/kg/min
None	1.1-3.3	0.5-1.5	30-60	1.1-3.3	0.11-0.33
Acepromazine	1.1	0.5	30-60	1.1-2.2	0.11-0.22
Xylazine	1.1	0.5	30-60	1.1-2.2	0.11-0.22
Oxymorphone	1.1	0.5	30-60	1.1-2.2	0.11-0.22
Medetomidine	1.1	0.5	30-60	1.1-2.2	0.11-0.22
Butorphanol	1.5	0.7	30-60	1.5-3.0	0.15-0.30
Acepromazine/ Butorphanol	1.1	0.5	30-60	1.1-2.2	0.11-0.22

Repeated maintenance doses of propofol does not result in increased recovery times, indicating that the anesthetic effects of propofol are not cumulative.

2) Maintenance by Inhalant Anesthetics:

Clinical trials using propofol have shown that it may be necessary to use a higher initial concentration of the inhalant anesthetic than is usually required following induction using barbiturate anesthetics, due to rapid recovery from RAPINOVET.

4. Effectiveness:

The efficacy of propofol was demonstrated in three pivotal studies:

a. Dose Determination Study:

Phase 1: Propofol Alone for Induction of Anesthesia
Phase 2: Propofol Alone for Maintenance of Anesthesia

b. Compatibility of Propofol in Dogs When Used with Preanesthetics and Inhalant Anesthetics

c. Clinical Trial Under Field Conditions with Propofol in Dogs

a. DOSE DETERMINATION STUDY: INDUCTION PHASE 1:

Investigator:
Dr. Charles E. Short
Cornell University College of Veterinary Medicine
Department of Clinical Sciences
Ithaca, NY 14853-6401

Sponsor Monitors:
Dr. Darrell Salsbury
Dr. Donald Campbell
Mallinckrodt Veterinary, Inc.
421 East Hawley Street
Mundelein, IL 60060

The objective of the study was to determine an effective induction dose and the mean duration of anesthesia in dogs. The formulation for the injectable anesthetic was the same as the market formulation. Placebo controls were not used due to the nature of the drug being investigated (anesthetic). Each dog served as its own control in that it was either anesthetized or not anesthetized as determined by reflex response to tail clamp, purposeful movements, or other clinical observations.

Short and Salsbury (1994a) conducted the induction dose determination study in 30 mongrel dogs. The dogs were divided into 3 groups of 5 males and 5 females each. Propofol was administered as a single intravenous dose of 3.3, 6.6, or 9.9 mg/kg delivered during periods of approximately 25, 60, or 90 seconds, respectively (dose rate approximately 6.6 mg/kg/min). Observations included induction time, duration of anesthesia, recovery time, respiratory rate, pulse rate, mean arterial blood pressure, oxygen saturation, and adverse reactions. Most dogs received routine supplemental oxygen when oxygen saturation levels decreased below 90%.

RESULTS:

DURATION OF ANESTHESIA:

The following table lists the individual values for duration of anesthesia for each dose group:
Duration of Anesthesia vs. Dose:

3.3 mg/kg	6.6 mg/kg	9.9 mg/kg
range 0-3.01 min	range 2.35-11.02 min	range 5.53-23.46 min
0 min	7.05 min	12.39 min
0	6.58	10.59
3.01	10.03	15.55
0	9.54	5.53
0	4.01	14.05
0	3.12	10.02
0	11.02	16.14
2.03	2.35	12.11
1.03	5.24	9.00
0	5.04	23.46

The 3.3 mg/kg dose failed to induce anesthesia in some dogs (7 of 10).
The dose of 6.6 mg/kg demonstrated adequate periods of anesthesia without apnea.
The mean duration of anesthesia was 6 minutes and 32 seconds (6:32; range 2:35 - 11:02).

Duration of anesthesia was significantly longer ($p < 0.05$) in the 9.9 mg/kg dose group than in the 6.6 mg/kg dose group by Kruskal-Wallis test. However, despite oxygen supplementation (administered when oxygen saturation decreased below 90%), four dogs experienced apnea among the 10 dogs in the 9.9 mg/kg dose group compared to none in the 6.6 mg/kg dose group. This difference was statistically significant by the Fisher's Exact test ($p < 0.05$). Based upon these results, the 9.9 mg/kg dose produced excessive anesthesia as judged by the occurrence of apnea in four dogs (severe in three dogs).

RECOVERY TIME:

The following table lists individual recovery times in minutes (beginning of anesthesia until standing recovery) for each dose group:

Recovery Time vs. Dose:

3.3 mg/kg	6.6 mg/kg	9.9 mg/kg
range 7.08-20.56 min	range 12.20-28.06	range 16.41-83.41
7.08 min	22.33 min	18.59 min
12.32	22.25	25.38
7.59	22.31	29.04
20.56	21.33	23.55
13.45	21.01	27.47
7.29	13.57	19.19
17.14	28.06	19.44
7.16	17.59	22.01
18.22	21.51	16.41
18.26	12.20	83.41

In the 6.6 mg/kg group, the mean time from end of anesthesia to full standing recovery was 13:54 minutes:seconds (range 7:16 - 17:00). One dog in the 9.9 mg/kg dose group experienced an excessively long recovery period.

HEART RATE (HR):

There was a tendency for HR to increase immediately after induction (increase in rate with normal sinus rhythm). No cardiac arrhythmias were observed.

RESPIRATORY RATE (RR):

Respiration rates generally decreased following administration of propofol, especially at two minutes post-induction. There was conclusive evidence of respiratory depression (RR < 8 breaths/minute) in the 9.9 mg/kg dose group. Four dogs in this group experienced apnea, three of which were severe (> 5 minutes). Respiratory depression was also seen in the 6.6 mg/kg dose group but was of short duration.

OXYGEN SATURATION:

Oxygen supplementation was administered when oxygen saturation decreased below 90%. In the 6.6 mg/kg group, values returned to normal when the animals were given supplemental oxygen. No adverse reactions were noted in the 6.6 mg/kg group. Three

dogs in the 9.9 mg/kg dose group required assisted ventilation as well as supplemental oxygen.

BLOOD PRESSURE (BP):

BP measurements were within physiologically acceptable ranges and were adequately maintained during anesthesia.

CONCLUSION:

Based upon these results, the recommended dose of propofol for induction of anesthesia is 6.6 mg/kg, delivered at an even rate over 60 - 90 seconds.

a. DOSE DETERMINATION STUDY: MAINTENANCE PHASE 2:

Investigator:
Dr. Charles E. Short
Cornell University College of Veterinary Medicine
Department of Clinical Sciences
Ithaca, NY 14853-6401

Sponsor Monitors:
Dr. Darrell Salsbury
Dr. Donald Campbell
Mallinckrodt Veterinary, Inc.
421 East Hawley Street
Mundelein, IL 60060

Short and Salsbury (1994b) conducted a maintenance dose titration study in 30 mongrel dogs. The dogs were divided into 3 groups of 5 males and 5 females each. Propofol was administered to all dogs as a single induction dose at 6.6 mg/kg, delivered during a period of approximately 60 seconds. When each animal started to recover from anesthesia (by reacting to tail clamping, purposeful movements or other clinical signs), a maintenance dose of propofol was administered. This procedure was repeated as necessary until the dog had been anesthetized for a total of 30 minutes. Doses selected were 1.1, 3.3, and 5.5 mg/kg, given during 30, 60, or 90 seconds, respectively. Observations included induction time, duration of anesthesia, and recovery time; number of doses and dose volume; respiratory rate; pulse rate; mean arterial blood pressure; oxygen saturation; and adverse reactions. All dogs received supplemental oxygen during the study at least once (when oxygen saturation < 90%). The observers in the Phase 2 Maintenance Dose study were not blinded to the maintenance dose that was administered since parameters could be measured objectively or evaluated as "yes" or "no", and the animals served as their own controls.

RESULTS:

ANESTHESIA:

In the 1.1 mg/kg maintenance dose group, the average number of maintenance doses required for 30 minutes anesthesia was 9.9 (range 7 - 15), and the average time from the end of anesthesia to full standing recovery was 16 min:50 sec (range 8:17 - 27:37).

An average of 3.6 doses was required (range 3 - 5) for 30 minutes of anesthesia in the 3.3 mg/kg dose group, and the average time from the end of anesthesia to full standing recovery was 15:17 (range 7:05 - 25:44).

Recovery times did not differ between the 1.1 and 3.3 mg/kg dose groups.

APNEA:
The following table shows the occurrence of apnea during induction (6.6 mg/kg) and during maintenance for each of the maintenance dose groups:

Maintenance Dose Group	Apnea (induction) Dose = 6.6 mg/kg	Apnea during Maintenance
1.1 mg/kg	3	1
3.3 mg/kg	0	3
5.5 mg/kg	3	8*

* four dogs required IPPV

Six of 30 dogs experienced apnea during induction (6.6 mg/kg). Four dogs experienced apnea in either the 1.1 mg/kg maintenance group (1 dog) or in the 3.3 mg/kg group (3 dogs). Eight of 10 dogs experienced apnea in the 5.5 mg/kg maintenance group.

The 5.5 mg/kg supplemental dose produced excessive respiratory depression as judged by apnea in 8 of 10 dogs. Four of the 8 dogs required intermittent positive pressure ventilation (IPPV). Apnea precluded the administration of another maintenance dose of 5.5 mg/kg at the first sign of incomplete anesthesia in these 8 dogs. The number of occurrences of apnea in this group was statistically significantly more than in the two lower maintenance dose groups.

HEART RATE AND BLOOD PRESSURE:

Physiological responses were similar to those observed during the induction dose titration study (within acceptable ranges).

SIDE EFFECTS:

Apnea is the most common side effect associated with the administration of propofol. All dogs received and responded to the receipt of supplemental oxygen.

Other side effects noted during the study included inadequate muscle relaxation (one during induction and one during recovery) and opisthotonos during recovery (two). Measurement of all parameters could not be accomplished in two dogs in the 1.1 mg/kg dose group due to insufficient duration of anesthesia.

CONCLUSION:

Based on these results, anesthesia can be maintained with propofol in the range of 1.1 - 3.3 mg/kg, delivered at an even rate over a period of approximately 30 - 60 seconds (depending on dose). The duration of anesthesia can be regulated by selection of the dose (lower doses for shorter duration; higher doses for longer duration).

b. COMPATIBILITY OF PROPOFOL IN DOGS WHEN USED WITH PREANESTHETICS AND INHALANT ANESTHETICS

Study Director:
Charles E. Short, DVM, MS, PhD, Diplomate ACVA
Professor of Anesthesiology
Cornell University College of Veterinary Medicine
Ithaca, NY 14853-6401

Assistant Investigators at Cornell University:

Susan Miller, DVM
Antonello Bufalari, DVM
Claudia Bufalari, DVM

Test Facility:

Department of Clinical Sciences
College of Veterinary Medicine
Cornell University
Ithaca, NY 14853-6401
Study Dates: May, 1993-July, 1994

Sponsor Monitors:
Dr. Darrell Salsbury
Dr. Donald Campbell
Mallinckrodt Veterinary, Inc.
421 East Hawley Street
Mundelein, IL 60060

Short and Campbell (1995) conducted a sequential series of drug trials on the compatibility of propofol when used in combination with various pre-anesthetics for induction of anesthesia.

OBJECTIVE: To determine the pharmacophysiological responses to propofol when used in conjunction with various preanesthetics and when used as an induction agent to inhalational anesthetics.

STUDY DESIGN:

Thirty-six mongrel dogs (18 males and 18 females) approximately one year old and 33-65 pounds were used in the study. The same dogs had been previously used in the dose determination studies (P210-007 and P210-008). Each dog was used approximately three times (range 1-5 times) during the study.

Each of 17 groups contained 6 dogs. One group each was premedicated with atropine, glycopyrrolate, acepromazine, diazepam, oxymorphone, xylazine, and butorphanol; medetomidine was administered at two levels. One group received both acepromazine and butorphanol prior to propofol. The dose for propofol was reduced in most groups depending on the sedative effect of the premedicant. The reduction in induction dose of propofol was selected based upon knowledge of drug mechanisms of action or experience with the pre-anesthetic drug(s) in combination with other anesthetics. Induction and recovery times were compared to results from Phase I (induction using propofol only) of the dose determination study.

Three groups received propofol as an induction agent and were maintained for 30 minutes using halothane, isoflurane, or methoxyflurane. Three other groups were pretreated with atropine, atropine plus acepromazine, or atropine plus medetomidine, then induced and maintained with propofol for 30 minutes. Induction and recovery times were compared to results from Phase II (propofol maintenance) of the dose determination study. The compatibility study was not blinded.

Observations included induction time, duration of anesthesia, recovery time, pulse (HR), respiration rate (RR), systolic, diastolic, and mean arterial blood pressure (BP), oxygen saturation, electroencephalograms (EEG for propofol and inhalant maintenance groups only), and adverse reactions.

Propofol was administered slowly IV over 15 to 65 seconds, depending on the dose. For example, a dose of 2.2 mg/kg was given over 20 seconds; a dose of 6.6 mg/kg was administered over 60 seconds.

Treatment Groups:

Group	**Drug**	**Dose**
1	propofol	6.6 mg/kgIV
	atropine	0.04 mg/kg IM
2	propofol	6.6 mg/kg IV
	glycopyr	0.01 mg/kg IM
3	propofol	4.4 mg/kg IV
	acepromaz	0.1 mg/kg IM
4	propofol	4.4 mg/kg IV
	diazepam	0.2 mg/kg IV
5	propofol	3.3 mg/kg IV
	oxymorph	0.1 mg/kg IV
6	propofol	3.3 mg/kg IV
	medetom	5 ug/kg IM
	atropine	0.02 mg/kg IM
7	propofol	2.2 mg/kg IV
	medetom	10 ug/kg IM
	atropine	0.02 mg/kg IM
7.2^	propofol	2.2 mg/kg IV
	medetom	10 ug/kg IM
	atropine	0.2 mg/kg IM
	atipamezole	30 ug/kg IV
8	propofol	2.2 mg/kg IV
	xylazine	0.5 mg/kg IM
9	propofol	6.6 mg/kg IV
	isoflurane	0.6-2.5% *
	oxygen	2 L/min
10	propofol	6.6 mg/kg IV
	methoxyfl	0.1-0.5%*
	oxygen	2 L/min
11	propofol	6.6 mg/kg IV
	halothane	0.5-1.8%*
	oxygen	2 L/min
12	atropine	0.02 mg/kg IM
	propofol	6.6 mg/kg IV#
	propofol	1.1 mg/kg IV@
13	atropine	0.02 mg/kg IM
	acepromaz	0.1 mg/kg IM
	propofol	4.4 mg/kg IV#
	propofol	1.1 mg/kg IV@
14	atropine	0.02 mg/kg IM
	medetom	10 ug/kg IM
	propofol	2.2 mg/kg IV#
	propofol	1.1 mg/kg IV@
15	butorphan	0.2 mg/kg IM
	propofol	4.4 mg/kg IV
16	acepromaz	0.1 mg/kg IM
	butorphan	0.2 mg/kg IM
	propofol	3.3 mg/kg IV

* or as the inhalant anesthetic was required (to effect)
# propofol as induction dose
@ multiple dose propofol maintenance
^group 7 was repeated using atipamezole for medetomidine reversal

RESULTS:
All dogs in all groups were adequately anesthetized with propofol, with one exception (one was refractive to acepromazine). Medetomidine premedicated dogs received low induction doses of propofol (2.2 mg/kg) and frequently required another low dose of propofol (1.1 mg/kg) to be successfully intubated. No dogs in any groups died, and no uncontrollable adverse reactions were observed.

Duration of anesthesia is the time elapsed from the beginning of anesthesia and does not include premedicant or induction times. Recovery times were calculated by subtracting "walk" time (standing recovery) from "sleep" (anesthesia) times.

The following results are grouped according to type of premedicant (anticholinergic, tranquilizer, etc.); therefore, the group numbers are not in order. Conclusions were drawn from inspection of the means of the observed variables for each group. In general, physiological effects were dependent on the premedicant that was administered.

Anticholinergics:

Either atropine (group 1) or glycopyrrolate (group 2) were given 15 minutes before propofol induction. Propofol was given at 6.6 mg/kg over 60 seconds. All dogs were anesthetized.

The following table shows average values in minutes for the duration of anesthesia and recovery times for groups 1 and 2 compared to results from Phase I of the dose determination study.

Group	**Duration of Anesthesia**	**Recovery Time**
Phase I (propofol only)	6.53 min	13.90 min
Group 1	8.26 min	13.95 min
Group 2	8.47 min	11.65 min

Duration of anesthesia and recovery times were not different between groups 1 and 2, and were similar to the duration and recovery times observed during Phase I (induction only) of the dose determination study.

Physiological responses were unremarkable except for an expected increase in heart rate (HR). Increases in HR were greater using atropine; no arrhythmias were noted on the ECG monitor and no adverse effects observed.

Apnea occurred in one atropine treated dog and all dogs developed respiratory depression observed as a reduction in oxygen saturation below 90%. These side effects are due to propofol and not to the anticholinergics and all dogs responded to oxygen administration.

Tranquilizers (acepromazine, diazepam) or Sedatives (xylazine, alpha-2-agonist):
Three groups of six dogs each were premedicated as follows:

Group 3 (acepromazine): propofol dose reduced to 4.4 mg/kg
Group 4 (diazepam): propofol dose reduced to 4.4 mg/kg
Group 8 (xylazine): propofol dose reduced to 2.2 mg/kg

The following table shows average values in minutes for the duration of anesthesia and recovery times for groups 3, 4, and 8 compared to results from Phase I of the dose determination study.

Group	**Duration of Anes**	**Recovery Time**
Phase I (propofol only)	6.53 min	13.90
3 (acepromazine)	9.23	25.83
4 (diazepam)	5.94	13.87
8 (xylazine)	11.31	32.91

Premedication with diazepam coupled with a reduced propofol induction dose (4.4 mg/kg, 33% reduction in propofol dose) resulted in anesthesia and recovery times similar to groups that did not receive tranquilizing agents (as in groups 1 and 2).

Premedication with acepromazine was not associated with a prolongation of anesthesia time at the reduced propofol dose (4.4 mg/kg, 33% reduction in propofol dose); however, recovery time was slower.

Duration of anesthesia and recovery times were both lengthened following premedication with xylazine (propofol dose = 2.2 mg/kg, 67% reduction in propofol dose).

Sedative-medetomidine (alpha-2-agonist):

Two groups of six dogs each and one group of five dogs were premedicated as follows:

Group 6 (5 ug/kg medetomidine IM): propofol dose 3.3 mg/kg (50% reduction)
Group 7 (10 ug/kg medetomidine IM): propofol dose 2.2 mg/kg (67% reduction)
Group 7.2 (10 ug/kg medetomidine IM): propofol dose 2.2 mg/kg (67% reduction)
Atipamezole reversal (30 ug IV) of group 7.2 occurred after 30 minutes of observations.
Atropine was given to all three groups (0.02 mg/kg) to prevent bradycardia.

Effects on anesthetic parameters of medetomidine with propofol induction:

The following tables show the individual duration of anesthesia and recovery times for dogs in groups 6, 7, and 7.2 in minutes:seconds.

Dog Number	**Duration of Anes**	**Recovery Time**
Group 6 (5 ug IM)		
87408	8 min 20 seconds	33'38"
86509	26'	37'23"
86444	18'47"	1'63"
87157	8'53"	24'12"
79120	0	13'24"
86452	17'40"	21'29"
Averages	13'16"	23'45"

Dog Number	**Duration of Anes**	**Recovery Time**
Group 7 (10 ug IM)		
86339	2'	81'44"
79529	14'18"	49'
84921	6'	2'51"
81949	16'28"	54'46"
86461	20'40"	31'45"
87084	12'40"	48'34"
Averages	12'6"	44'49"

Dog Number	**Duration of Anes**	**Recovery Time***
Group 7.2 (10 ug IM)		
79642	36'	2'10"
81949	26'	13'41"
82031	10'	30'20"
86444	15'	19'49"
84794	18'12"	19'31"
86991	10'	26'40"
Averages	19'12"	18'44"

*Medetomidine was reversed using atipamezole after 30 minutes resulting in much shorter recovery times compared to group 7.

Anesthetic duration was similar to dogs that received xylazine (see above). Recovery times were similar for xylazine and the lower dose of medetomidine (33’31”, 23’45” respectively). Dogs that received the higher medetomidine dose experienced prolonged recovery times (44”49’).

Group 6: The propofol dose for one dog in the 5 ug medetomidine group (#79120) was insufficient for anesthesia and intubation. Recovery time was also short for this dog (13.4 minutes) compared to the other dogs in the group.

Group 7: Two dogs in the 10 ug medetomidine group were not intubated due to insufficient anesthesia (79529 & 84921); one of these (84921) did not reach an adequate level of surgical anesthesia (determined by response to tail clamp). This dog also had a short recovery time (compared to others in group 7). The other dog (79529) experienced a delayed response until anesthesia.

Group 7.2: One dog was not sufficiently anesthetized for intubation (86991)

Recommendations:

The propofol dose of 3.3 mg/kg with 5 ug/kg of IM medetomidine premedication and the propofol dose of 2.2 mg/kg with 10 ug/kg of IM medetomidine premedication is sometimes insufficient to induce a surgical level of anesthesia and allow intubation. A higher routine initial propofol induction bolus dose of 3.3 mg/kg was recommended by the investigator if the larger propofol dose is not administered too rapidly. Slow administration (30-60 seconds) should prevent severe respiratory depression. Alternatively, the investigator recommends that an additional 1 mg/kg of propofol could be administered, but only if the induction dose is insufficient. However, these recommendations are not based on the results of this study. This method of induction

has been used successfully in the literature and in the clinical trial (see below) using other premedicants (not medetomidine) with propofol when anesthesia has been insufficient for intubation. Note that additional low doses of propofol may cause apnea.

Physiological effects of medetomidine premedication with propofol induction:

As expected, medetomidine initiated a rise in BP. These changes were within acceptable limits. Increases in HR and respiratory depression due to propofol were also within acceptable limits. The use of oxygen enriched air was beneficial and increased oxygen saturation of hemoglobin. One dog in group 7 experienced ventricular tachycardia for approximately two minutes, elevated HR, and pulsas alternans (alternation in the height of the R and T waves). The investigator did not attribute this to the direct effect of premedication or anesthesia.

Atipamezole reversal of medetomidine:

Administration of atipamezole after the end of anesthesia (group 7.2) reversed the effects of medetomidine (including analgesia), reducing recovery time compared to the medetomidine group where sedation was allowed to continue (group 7).

Overall conclusion on groups 6, 7 &7.2:

Physiologically, atropine, medetomidine, and propofol were compatible at the doses used in the study. Anesthetically, medetomidine preanesthesia to propofol anesthesia resulted in longer anesthesia times (anesthesia times similar to xylazine and oxymorphone). Recovery times were also longer because sedation from medetomidine lasted longer than propofol anesthesia, especially at the higher medetomidine dose. Longer recovery times were reversible using atipamezole. Apnea occurred infrequently and recoveries were smooth and safe. Insufficient anesthesia during intubation may occur using lowered propofol doses and IM medetomidine preanesthesia.

Analgesics - Opioid Agonist, Opioid Agonist/Antagonist:

Two groups of six dogs each were premedicated as follows:

Group 5 (oxymorphone, opioid agonist): propofol dose reduced to 3.3 mg/kg
Group 15 (butorphanol, opioid agonist/antagonist): propofol dose reduced to 4.4 mg/kg

All 12 dogs were anesthetized with evidence of analgesia (as determined by oximeter probe on tongue).

The following table shows average values in minutes for the duration of anesthesia and recovery times for groups 5 and 6 compared to results from Phase I of the dose determination study.

Group	**Duration of Anes**	**Recovery Time**
Phase I (propofol only)	6.53 min	13.90
5 (oxymorphone)	10.57	52.2
15 (butorphanol)	10.6	25.9

Longer anesthesia times and much longer recovery times were seen using oxymorphone with 50% the propofol dose (3.3 mg/kg). Elevated RR was seen following premedication with oxymorphone (and panting) prior to the administration of propofol. This effect is a reflection of the opioid agonist itself.

Butorphanol followed by a lower propofol dose (4.4 mg/kg) lowered respiratory rates. Oxygen saturation decreased with both premedicants, but to a greater degree with oxymorphone; however, dogs responded satisfactorily in both groups to supplemental oxygen.

HR decreased after administration of both premedicants, then increased following induction with propofol. BP increased after premedication, then decreased following propofol (lowest at 10 minutes after propofol). BP remained at acceptable levels and dogs did not require treatment for hypotension.

Analgesia lasted longer using oxymorphone compared to butorphanol as determined by toleration of the oximeter probe on the tongue (15 min butorphanol, 35 min oxymorphone).

Conclusion:

Propofol requirements were reduced by premedication with analgesics. Both duration of anesthesia and recovery times were increased, depending on the premedicant. Analgesia was increased with some premedicants compared to using propofol alone, especially with oxymorphone.

Tranquilizer and Analgesic (acepromazine, butorphanol):

One group of six dogs (group 16) was premedicated with acepromazine and butorphanol, followed by propofol induction at 3.3 mg/kg (50% decrease in induction dose).

The use of a tranquilizer and an opioid results in neuroleptanalgesia. More profound analgesia is seen than with the use of either premedicant alone (less response to tail cross clamp). The use of these premedicants also greatly reduced the dose of anesthetic that was needed. The duration of anesthesia and recovery time are also prolonged as seen in the following table of average values:

Group	**Duration of Anes**	**Recovery Time**
Phase I (propofol only)	6.53 min	13.90 min
16 (ace, butorphanol)	15.14	51.6
3 (acepromazine)	9.23	25.83
15 (butorphanol)	10.6	25.9

Duration of anesthesia and recovery time were both increased when the two premedicants were used in conjunction, compared to using butorphanol (group 15) or acepromazine (group 3) as the sole premedicant.

The use of both premedicants also had more profound cardiovascular effects than the use of either premedicant alone. Lower BP continued longer in group 16 (for 45 minutes). No adverse effects associated with hypotension occurred.

Four of six dogs experienced apnea and received oxygen supplementation following induction with propofol following acepromazine/butorphanol premedication. Four of six dogs also experienced apnea following induction with butorphanol/propofol; however, the propofol dose was higher. Apnea was not as common in the acepromazine/propofol group (one in five dogs).

Conclusion:

The use of acepromazine/butorphanol prior to propofol is more likely to cause respiratory depression than either single premedicant. This combination also lengthens anesthesia, recovery, and provides more profound analgesia.

The results described for the dose groups above showed that the use of propofol for induction of anesthesia, under clinically relevant conditions utilizing preanesthetic agents that are likely to be used in the field, is safe and effective when dosage levels of propofol have been appropriately adjusted.

Anesthesia Maintenance with Propofol:

Three groups of six dogs were anesthetized as follows:

Group	**Premedicants**	**Propofol Induction**
12	atropine 0.02 mg/kg IM	6.6 mg/kg IV (over 60 sec)
13	atropine 0.02 mg/kg IM acepromazine 0.1 mg/kg IM	4.4 mg/kg IV (over 40 sec)
14	atropine 0.02 mg/kg IM medetomidine 10 ug/kg IM	2.2 mg/kg IV (over 20 sec)

Atropine was given 20 minutes before anesthetic induction. Acepromazine or medetomidine were given 15 minutes before induction. Maintenance doses of propofol (1.1 mg/kg IV) were given as needed for 30 minutes. RR, $C0_2$, HR, BP, and body temperature were recorded. EEG and oxygen saturation measurements were begun at 2 minutes after propofol induction.

ANESTHESIA EFFECTS:

In these three groups, neurologically equivalent levels of anesthesia were established using propofol as determined by electroencephalographic analyses. Decreased amplitude can be correlated with a neurologically surgical plane of anesthesia (Short, C. The effects of selective alpha-2-adrenoreceptor agonists on cardiovascular and pulmonary functions and brain wave activity in horses and dogs. Veterinary Practice Publishing Company, Santa Barbara, CA (1991), p. 13). The EEG recordings coupled with a subjective pain stimulus (tail clamp) indicated that adequate equipotent anesthesia was achieved in all three groups.

The following table shows average values in minutes for the duration of anesthesia and recovery times for groups 12, 13, and 14 compared to results from Phase 2 (maintenance) of the dose determination study.

Groups	**Duration of Anes***	**Recovery Time**
Phase 2 (propofol only)	32.1 minutes	15.83 minutes
group 12 (atrop, prop)	33.5	9.5
group 13 (atrop, ace, prop)	32.1	16.5
group 14 (atrop, medet, propofol)	38.9	32.9

*Dogs received maintenance boluses of propofol for 30 minutes.

Recovery times were comparable between groups12 and 13, and much longer in group 14. Recovery times reflect the influence of the premedicant that was used.

The following table shows the influence of preanesthesia on propofol maintenance requirements.

Group	**No. of Repeat Doses**	**Mean Minutes Between Doses**
12	5.8 (4-8 range)	6:05 (min/sec)
13	5.7 (2-8)	7:21
14	4.5 (3-8)	10:15

The frequency of supplemental doses reflects the effects of premedication. Premedication with medetomidine results in longer intervals between maintenance doses and longer recovery times compared to pretreatment with acepromazine or atropine alone.

Three (of six) dogs in the medetomidine group could not be intubated using 2.2 mg/kg propofol IV, but were intubated after an additional 1.1 mg/kg propofol was administered (see additional comments concerning insufficient anesthesia using medetomidine and propofol under the discussion of groups 6, 7, and 7.2 above).

PHYSIOLOGICAL PARAMETERS:

Cardiovascular: Atropine increased the HR in all three groups, peaking at the time of propofol induction (15 minutes after atropine administration) and subsequently declining. BP declined slightly after induction in groups 12 and 13. No differences were noted in BP between these two groups.

BP was continuously elevated during the entire anesthetic period in group 14, peaking at 10-15 post-propofol and then slowly declining. Medetomidine administration causes a rise in BP (initial vasopressor response due to vasoconstriction). The bradycardia that is seen in dogs receiving medetomidine alone is probably a reflex response to this hypertension. Since atropine prevented this bradycardia, the hypertension was prolonged. The investigator believes that BP in this group would have returned to baseline levels within 30 minutes if atropine had not been administered as well as medetomidine. Cardiovascular problems associated with the use of atropine in conjunction with medetomidine are partially discussed on the medetomidine label under Precautions.

RR: RR were elevated in group 12, and stable in groups 13 and 14. One dog in group 12 experienced apnea after propofol induction. Apnea was resolved within six minutes using oxygen and manual intermittent positive pressure ventilation (IPPV). Other significant drops in RR of clinical concern were not observed.

Oxygen saturation: All dogs received oxygen since all oxygen saturation levels decreased below 90%; therefore, the values reflect the use of oxygen as needed to maintain saturation at greater than 90%. Initial oxygen saturation levels indicate that medetomidine treated dogs experienced greater respiratory depression.

Body Temperature: All dogs showed an expected drop in temperature by an average of 2.3 degrees F.

Anesthesia Maintenance with Inhalant Anesthetics:

Three groups of six dogs each were anesthetized as follows:

Group 9: propofol induction dose 6.6 mg/kg, isoflurane maintenance
Group 10: propofol induction dose 6.6 mg/kg, methoxyflurane maintenance
Group 11: propofol induction dose 6.6 mg/kg, halothane maintenance

Dogs were induced with propofol, intubated, and breathed oxygen until the 2 minute post-propofol measurements were made. Dogs were then maintained on inhalant anesthetics for 30 minutes as follows:
Methoxyflurane: Ohio #8 in-circle vaporizer
Isoflurane and Halothane: precision out-of-circle vaporizers

In addition to the other clinical and physiological measurements, electroencephalograms (EEGs) were also recorded for these three groups. EEG results demonstrated a neurologically surgical plane of anesthesia with the use of the inhalant anesthetics. This parameter did not provide any relevant data with regard to propofol and is therefore not discussed in this FOI Summary.

ANESTHETIC EFFECTS:

The following table shows average values in minutes for the duration of anesthesia and recovery times for groups 9, 10, and 11.

Groups	**Duration of Anes**	**Recovery Time**
group 9 (isoflurane)	39.1 minutes	10.1 minutes
group 10 (methoxyflurane)	46.5	5.4
group 11 (halothane)	43.16	5.7

Dogs in groups 9, 10, and 11 received inhalant maintenance anesthesia for 30 minutes. Induction and intubation was achieved in all three groups. There was a problem regarding the transition from propofol induction to methoxyflurane anesthesia. All dogs partially aroused from anesthesia before they stabilized on methoxyflurane (2-5 minutes after propofol injection). This problem could probably have been avoided if

methoxyflurane had been administered immediately after induction (instead of waiting until the two minute propofol measurements were made). Recovery from propofol was too rapid to allow for inhalation of adequate concentrations of methoxyflurane. This was not a problem with isoflurane or halothane. Once adequate concentrations had been inhaled, anesthesia was satisfactorily maintained in the methoxyflurane group.

PHYSIOLOGICAL PARAMETERS:

HR: As expected, HR increased following propofol induction, then decreased during inhalant maintenance, with no problems noted.

BP: Mean arterial BP was higher during propofol anesthesia than with the inhalants. BP were acceptable during inhalant maintenance and responded to adjustment of the inhalant concentrations.

RR: The most profound respiratory depression was seen immediately after propofol induction.

Oxygen saturation was slightly reduced after propofol, and was corrected and stabilized after oxygen and inhalant administration. Some $C0_2$ accumulation was observed during methoxyflurane anesthesia; this was a response to both propofol and methoxyflurane.

Conclusion on Groups 9, 10, and 11:

Compatibility of propofol with the three inhalant anesthetics was demonstrated. It is probable that induction and adequate maintenance anesthesia using methoxyflurane will be possible under field conditions when the inhalant is administered immediately after propofol induction and preanesthetics are used. Physiological parameters and recovery times were satisfactory. Based on these results, propofol is safe and effective for induction of anesthesia that will be maintained by an inhalant.

ADVERSE REACTIONS DURING COMPATIBILITY STUDY:

No dogs died during the study. No uncontrollable adverse reactions were observed. All animals received oxygen routinely and IPPV was available. Apnea occurred infrequently and as expected was the most common adverse event (16 times in 102 anesthetic episodes).

Nine dogs could not be intubated because of insufficient anesthesia. All of these dogs (9 of 24) received IM medetomidine as a preanesthetic prior to the lowest propofol induction dose (2.2 mg/kg). Inability to intubate occurred in all four medetomidine groups (6, 7, 7.2, and 14). An additional 1.1 mg/kg of propofol allowed intubation to be achieved easily in all instances.

Other minor adverse reactions occurred, included paddling, muscle tremors, muscle rigidity, panting, and slow recovery. Slow recoveries were related to premedication, not to propofol.

One dog in group 7 (medetomidine, 10 ug/kg IM) experienced ventricular tachycardia for approximately two minutes, elevated HR, and pulsas alternans (alternation in the

height of the R and T waves). There was nothing in the dog's clinical records to explain the abnormality and there is no reason to associate its occurrence with either propofol or the premedicants.

c. CLINICAL TRIAL UNDER FIELD CONDITIONS WITH PROPOFOL IN DOGS:

Sponsor Monitor:
Dr. Kurt Peterson
Mallinckrodt Veterinary, Inc.
421 East Hawley Street
Mundelein, IL 60060

Clinical Investigators:

1. Animal Emergency Care, Inc. (AEC)
   Dr. Bernard Monahan
   Dr. Leann Pape

2. Bonham Veterinary Clinic (BVC)
   Dr. Eve Gerome
   Dr. Susan Miller

3. Brookside Animal Clinic (BAC)
   Dr. Teri Schenkelberg
   Dr. Steve Smith

4. Colorado State University (CSU)
   Dr. Jamie Gaynor
   Dr. Etta Wertz

5. Community Veterinary Hospital (CVH)
   Dr. William Grant II
   Dr. Grace Matsuura

6. Hoffman Estates Animal Clinic (HEAC)
   Dr. Ann Brooks
   Dr. Joy Dvorak
   Dr. Jeffrey House

7. Kildaire Animal Medical Center (KAMC)
   Dr. Nick Ashford
   Dr. Christine Boyd
   Dr. Michele Karl
   Dr. Dianna Shattuck
   Dr. John Strasser

8. Michigan State University (MSU)
   Dr. George Bohart
   Dr. Donald Sawyer

9. Ralston Veterinary Clinic (RVC)
   Dr. Allan Erickson
   Dr. Norman B. Jernigan

10. Vernon Hills Animal Hospital (VHAH)
Dr. Molly McCullough
Dr. Cheryl Roge

11. West Bay Animal Hospital (WBAH)
Dr. Daniel Simpson

Study Dates: April, 1995 to September, 1995

Objectives:

1. To evaluate the efficacy of propofol when administered:

   a. as the sole anesthetic agent in dogs (induction & maintenance).

   b. in conjunction with preanesthetic agents in dogs.

   c. for induction of anesthesia with subsequent maintenance by inhalant anesthetics.

2. To confirm the safety of propofol under clinical field conditions and identify the need for special label precautions.

Study Design:

The study included 325 dogs that were presented to veterinarians in private practice or at veterinary teaching hospitals for surgery and/or other procedures that required anesthesia. The study population was divided into three major treatment classifications:

1. propofol as the sole anesthetic, either as a single injection for induction, or with repeated administrations for maintenance anesthesia,

2. propofol induction in conjunction with various preanesthetics (acepromazine, oxymorphone, butorphanol, xylazine, and acepromazine/butorphanol), maintained if necessary with propofol or inhalant anesthetics,

3. propofol induction with subsequent maintenance by inhalant anesthetics (halothane or isoflurane).

Dogs were placed into treatment classifications by the investigator based on the length of the procedure, the type of surgery, the test facility capability, and occasionally the temperament of the dog. Intravenous catheters were utilized for 231 cases during the study.

Data recorded included information on the patients and procedures, objective and subjective anesthetic performance (ease of induction, duration and nature of anesthesia, duration and nature of recovery, overall satisfaction), physiological parameters (respiration rate, pulse rate, blood pressure), and adverse reactions.

A varied number of breeds (approximately 70) and crossbreeds were represented. The dogs ranged in age from two months to 16 years and in weight from 1.8 - 77.7 kilograms. The study included 180 males (intact and castrated), 144 females (intact and

spayed), and one where the sex was not indicated. There were instances when the same dog was anesthetized more than one time during the study, and these were considered a separate case each time. Of the 325 anesthetic episodes, 313 dogs were anesthetized once. Five dogs were used more than once, representing twelve anesthetic episodes.

The most prevalent concomitant therapies were those involving heartworm prevention. Other concomitant therapies included atropine, hydrazine, phenobarbital, and chloramphenicol.

Physical Status of Study Dogs:

The following table shows the number of dogs in each health classification as determined by physical examination (status is based on the American Society of Anesthesiologists/ASA rating):

Induction Regime	**# Dogs**	**ASA 1**	**ASA 2**	**ASA 3**	**ASA 4**
propofol only	42	30	9	3	-
propofol/acepromazine	47	41	5	1	-
propofol/oxymorphone	48	38	8	2	-
propofol/xylazine	41	38	3	-	-
propofol/butorphanol	24	17	5	2	-
prop/butorph/aceprom	24	22	1	1	-
propofol/halothane	51	40	10	1	-
propofol/isoflurane	48	44	2	1	1
totals	325	270	43	11	1

Dogs in the study were classified as ASA 1-4 with the following conditions:

ASA 1 (83%) = healthy without any apparent underlying condition.

ASA 2 (13%) = geriatric ± obesity, parasites, dehydration, or infection (n=21); heart murmurs (n=4); fever/infection (n=4); chronic gastrointestinal (GI) problems (n=2); recent wounds/injuries (n=2); pregnancy (n=2); dislocated hip (n=1); obesity only (n=1); previous recent surgery (n=1); idiopathic epilepsy (n=1); immune mediated or autoimmune gingivitis (n=1); possible embolism (n=1); hyperadrenocorticism (n=1); and mammary tumors (n=1).

ASA 3 (3%) = geriatric ± neoplasia, obesity, metabolic disease (n=4); chronic diabetes (n=1); heartworm disease (n=1); metabolic disease (n=1); pyelonephritis with grade III/IV systolic heart murmur and enlarged pancreas (n=1); severe intestinal parasitism with depression (n=1); and a slightly febrile and icteric dog with a testicular mass and enlarged prostate (n=1).

ASA 4 (one dog) = gastric dilatation and volvulus.

Procedures:

The most common procedures for which dogs were admitted to the study were castrations, ovariohysterectomies, dental cleanings, tumor removals, wound repair and X-rays. Multiple procedures were completed during anesthesia in some dogs. One

cesarean section was accomplished (xylazine/propofol/isoflurane), one total hip replacement (acepromazine/butorphanol/propofol/isoflurane), and one gastric dilatation/volvulus surgery (propofol/isoflurane).

The following table lists the procedures conducted, concomitant therapies, site, number of dogs (n), temperament (temp.) types (C=calm; N=nervous, excited; A=aggressive; and D=depressed), and the duration (mean and range) for procedures for each regimen (min:sec or hr:min:sec):

Regimen, (n), Procedure Duration(Mean & Range)	**Site**	**Temperament & n**	**Procedure & number**	**Concomitant Therapy & number**
Propofol Only n=42 7:50 0:06-23:24	BAC RVC VHAH HEAC BVC AEC CSU CVH MSU	C 20 N 16 A 1 D 4 N+A 1	X-rays plus 10 Aspirates/biopsies 5 Dental Plus 4 Castration 3 Suture/wound repair 3 Mass removal 3 Pedicure plus 2 Oral Exam 2 Ear lavage 1 CSF collection 1 Hardarian gland removal Avulsed toenail 1 removal 1 Cast leg 1 Porcupine quill removal 1 Fish hook removal 1 Grass awn removal 1 Flush and infuse anal glands 1 Tarsorrhaphy 1	Interceptor (milbemycin oxime) 3 Lactated Ringers 3 Heartgard (ivermectin) 2 Ophthaine 2 Paramite Dip 1 Cortaba 1 Flocillin 1 Baytril 1 Banamine 1 Gentocin o.o. 1 DA2PPVL 1 Flagyl 1 Meclofenamic acid 1 Aminophylline 1 Phenylpropanolamine 1 Thyrozine 1 Cefazolin 1 Cefoxitin 1
Propofol Acepromazine/ No maintenance n= 9 5:04 0:01-8:10	RVC VHAH CVH	C 5 N 4	X-rays plus 5 Pedicure plus 2 Suture removal 1 Remove piece of lacerated pad 1	Heartgard Plus 2 Program (lufenuron) 1 Aspirin 1
Propofol Acepromazine/ Propofol maintenance n=14 11:25 1:49-31:18	RVC VHAH BVC CVH	C 6 N 7 A 1	Castration 4 Dental/extractions 4 X-rays/exams 2 Tumor/cyst removal 2 Bandage and wound therapy 2	Aspirin 3 Cephalexin 2 Interceptor 1 Program 1 Dexamethasone 1 Filaribits Plus 1 Gentamicin 1

Regimen, (n), Procedure Duration(Mean & Range)	**Site**	**Temperament & n**	**Procedure & number**	**Concomitant Therapy & number**
Propofol Acepromazine/ Halothane maintenance n=13 44:08 9:27-2:29:39	BVC CSU CVH MSU	C 4 N 7 C+N 2	Spay 4 Dental/extractions 3 Castration 1 Dewclaw removal 1 Bronchoscopy 1 Wedge Trochlear. 1 Mass excision 1 Tarsal arthrodesis 1	Atropine 1 Amoxicillin 1 Interceptor 1 Soloxine 1
Propofol Acepromazine/ Isoflurane maintenance n=11 22:57 6:23-53:55	RVC VHAH CVH	C 3 N 7 A 1	Castration 5 Dental plus 2 Aural hematoma 2 Tonsillectomy 1 Spay 1	Heartgard 1 Program 1 Thyrozine 1
Propofol Oxymorphone/ No maintenance n=10 4:47 0:54-13:37	RVC CSU CVH MSU	C 5 N 4 D 1	X-rays +/- exam 6 Flush wound 1 Tumor removal 1 Dental 1 Nail trim 1	Heartgard 1 Cephalexin 1 Prednisone 1
Propofol Oxymorphone/ Propofol maintenance n=12 23:38 10:33-1:04:52	RVC CSU CVH MSU	C 4 N 8	Dental plus 3 Castration 1 Mass removal 1 Ear exam/cleaning 1 X-ray 1 Bronchoscopy 1 Wound closure 1 Vaginal endoscopy 1 Bandage change/ suture removal 1 Colonoscopy 1	Keflex 1 Oxycillin 1

Regimen, (n), Procedure Duration(Mean & Range)	**Site**	**Temperament & n**	**Procedure & number**	**Concomitant Therapy & number**
Propofol Oxymorphone/ Halothane maintenance n=13 1:20:42 9:11-4:18:32	CSU CVH MSU	C 5 N 8	X-rays plus 3 Castration plus 3 Dental 2 FLIT 1 Tumor removal 1 Spay 1 T-L myelogram 1 Skin biopsy 1	Heartgard 1
Propofol Oxymorphone/ Isoflurane maintenance n=13 55:08 13:27-2:17:38	RVC CSU CVH MSU	C 4 N 8 D 1	Dental plus 4 Castration plus 2 Spay 1 Bronchoscopy 1 Biopsy 1 Polyp removal 1 Oro-nasal fistula repair 1 Endoscopy 1 Modified retinacular imbrication 1	Thyrozine 2 Amoxicillin 1 Interceptor 1 Proanthazone 1 Adequan 1 Ascriptin 1 Clindamycin 1 Baytril 1 Antirobe 1 Clavomox 1 Tagamet 1 Reglan 1 Carafate 1
Propofol Xylazine/ No maintenance n=10 11:31 2:15-29:47	BAC BVC RVC CSU	C 2 N 5 A 3	Dental plus 4 Ear canal lavage 3 OFA X-ray 1 Vaginal cytology 1 Nail trim 1	Heartgard 1 Interceptor 1
Propofol Xylazine/ Propofol maintenance n=10 14:40 5:32-42:52	BAC RVC AEC CSU MSU	C 3 N 7	Dental 3 Castration 3 Porcupine quill removal 1 Toe nail removal 1 X-rays 1 Lumpectomy 1	Levothyroxine 1
Propofol Xylazine/ Halothane maintenance n=10 48:09 21:40-2:43:40	BVC CSU MSU	C 4 C 6	Castration 3 Spay 2 Orthopedic surgery 2 Dental 1 Tumor removal 1 Ear biopsy 1	Interceptor 3 Amoxicillin 3 Baytril 1 Lactated Ringers and dextrose 1 Program 1

Regimen, (n), Procedure Duration(Mean & Range)	**Site**	**Temperament & n**	**Procedure & number**	**Concomitant Therapy & number**
Propofol Xylazine/ Isoflurane maintenance n=11 49:00 7:29-2:32:13	BAC AEC CSU MSU	C 5 N 6	Dental 4 Orthopedic surgery 2 Cesarean section 1 Laceration repair 1 Mass removals 1 CSF tap plus 1 X-rays 1	Amoxicillin 1 Prednisone 1 Ascriptin 1
Propofol Butorphanol/ No or Propofol maintenance n=9 6:28 1:07-12:47	RVC CVH	C 3 N 6	X-rays 4 Castration 2 Extract teeth 1 Laceration repair 1 Remove wire 1	None
Propofol Butorphanol/ Halothane maintenance n=10 50:13 8:20-2:24:15	BVC CSU CVH	C 6 N 3 A 1	Dental plus 3 Spay 3 Castration 1 Cyst excision 1 Gastric tube placement 1 Otic lavage 1	Amoxicillin 2 Filaribits Plus 1 0.9% NaCl 1 Lactated Ringers 1 Baytril 1 Ampicillin 1 Adequan 1
Propofol Butorphanol/ Isoflurane maintenance n=5 52:25 12:12-1:21:44	RVC	C 5	Dental plus 2 Castration 1 Spay plus 1 Tumor removal 1	None
Propofol Butorphanol, Acepromazine/ No or propofol maintenance n=7 8:59 4:30-11:51	RVC CVH	C 5 N 2	Castration 3 X-rays 2 Nail trim 1 3rd eyelid flap repair 1	Cephalexin 1
Propofol Butorphanol, Acepromazine/ Halothane maintenance n=11 53:42 8:01-2:10:37	BVC CSU	C 2 N 9	Castration plus 5 Spay 2 X-rays 2 Tumor removal 1 Examine mouth 1	Amoxicillin 5 Interceptor 2 Atropine 1 Lactated Ringers 1 Gentamicin 1

Regimen, (n), Procedure Duration(Mean & Range)	**Site**	**Temperament & n**	**Procedure & number**	**Concomitant Therapy & number**
Propofol Butorphanol, acepromazine/ Isoflurane maintenance n=6 28:37 12:28-47:19	RVC MSU	C 2 N 4	Castration 2 Dental 2 Spay 1 Total hip replacement (THR) 1	Heartgard 2 Program 1 Ampicillin 1
Propofol Only/ Halothane maintenance n=51 32:12 4:48-1:59:03	KAMC HEAC BVC CVH	C 22 N 29	Dental plus 18 Spay plus 10 Castration plus 10 Tumor removal 4 Orthopedic surgery 4 X-rays 1 Anal gland removal 1 Suture repair 1 Bandage/recast 1 Digit amputation 1	Interceptor 20 Flocillin 10 Heartgard 9 Lactated Ringers 4 Program 3 Thyrozine 3 Derm Caps 2 Cephalexin 2 Soloxine 2 Filaribits Plus 2 Amoxicillin 2 Ascriptin 1 Hydroxyzine 1 Atropine 1 Phenobarbital 1
Propofol Only/ Isoflurane maintenance n=48 26:38 1:18:45	WBAH RVC VHAH HEAC AEC CVH	C 31 N 16 D 1	Castration plus 15 Dental plus 12 Spay plus 11 Tumor removal plus 4 Laceration repair 2 Aural hematoma 1 Orthopedic exam 1 3rd eyelid flap repair 1 GDV (gastic dila-tation volvulus surgery 1	Interceptor 10 Flocillin 7 Lactated Ringers 5 Program 2 Heartgard 2 Prednisone 2 Cefazolin 1 Amoxicillin 1 Paramite dip 1 Phenobarbital 1 Chloramphenicol 1 Cholodin 1 Potassium bromide 1 Cytomel 1 Digoxin 1 Thyrozine 1 Aminophylline 1 Enacard 1

INDUCTION OF ANESTHESIA:

Premedicant Treatment Groups:

Lists of the premedicant, number of animals treated with each premedicant, route of delivery, mean dose and dose range for each premedicant, the mean time and range of times between premedication and propofol induction are shown in the following table:

Preanesthetic Agent **n**	**Route of Delivery** **IM SQ** **n n**	**Mean Dosage (mg/kg)** **Dosage Range (mg/kg)**	**Mean Interval to Propofol (minutes)** **Range**
Acepromazine 47	20 27	0.1 0.02-0.77	49 9-154
Oxymorphone 48	24 24	0.1 0.09-0.11	52 13-295
Xylazine 41	30 11	0.52 0.33-1.1	36 0-117
Butorphanol 24	14 10	0.2 0.13-.26	40 10-65
Acepromazine/ Butorphanol 24	15 9	0.15 0.04-0.70 0.2 0.15-0.22	43 15-83

Most dogs received propofol between 20 and 60 minutes after premedication during the study. A wide range of time between premedication and administration of propofol affects the dosage and duration of propofol necessary for induction.

Premedicant doses are frequently lower than their label doses (see Thurmon et al., 1996, under References). Butorphanol is not approved for use in dogs at a concentration of 10 mg/mL (it is approved at 0.5 mg/mL), but it was included in the clinical trial because it is widely used (at the higher concentration) as a preanesthetic. Similar reasoning led to inclusion of acepromazine/butorphanol premedication. The use of the anticholinergic atropine was at the discretion of the investigators. Atropine was administered prior to propofol induction in 56 % of the cases.

The mean propofol induction doses (and ranges) for each treatment group and the mean dose rates of administration (and ranges) are shown in the following table:

Regimen	**n**	**Propofol Dose (mg/kg)** **Mean** **Range**	**Propofol Dose Rate (mg/kg/min)** **Mean** **Range**
Propofol Only	136	6.31 3.59-8.34	6.77 2.71-39.45
Acepromazine/ Propofol	46	4.19 2.64-5.87	3.74 1.25-5.87
Oxymorphone/ Propofol	47	3.31 1.43-5.90	2.92 1.19-4.95
Xylazine/ Propofol	41	2.75 1.94-8.01	2.34 0.55-7.02
Butorphanol/ Propofol	24	4.71 3.76-7.15	4.50 2.75-6.36
Acepromazine/ Butorphanol/ Propofol	24	2.37 1.52-4.42	2.27 1.45-4.42

Ease of Induction Scores were defined as follows:

Excellent = smooth, easily intubated
Good = needed up to 25% more propofol; otherwise smooth
Fair = required 25-50% more propofol; slight jaw tone, some movement
Poor = required ≥ more propofol; difficult to intubate, great amount jaw tone

Induction using propofol alone or with premedicants was mostly scored as excellent or good.

Scores	**Propofol only** **n=136**	**Ace/ Propofol** **n=46**	**Oxymor/ Propofol** **n=47**	**Xylazine / Propofol** **n=41**	**Butorph/ Propofol** **n=24**	**Ace/But / Propofol** **n=24**
Excellent	126 (93%)	44 (96%)	44 (94%)	27 (65%)	17 (70%)	20 (83%)
Good	7 (5%)	2 (4%)	2 (4%)	6 (15%)	5 (21%)	2 (8%)
Fair	3 (2%)		1 (2%)	3 (7%)	1 (4%)	2 (8%)
Poor				5 (12%)	1 (4%)	

Xylazine premedication resulted in 8 cases (of 41) as fair or poor. In the clinical trial protocol, the propofol dose following xylazine premedication was recommended as 2.2 mg/kg. Based on the results of the clinical trial, it may be necessary in some cases to increase the propofol dose to 3.3 mg/kg in order to improve induction. Based on these data, the labeling recommendation has been altered to a propofol dose of 2.2 to 3.3 mg/kg when xylazine is used as a premedicant. The time interval between premedication and propofol dosing is a key factor with this premedicant. The longer the interval between premedication and propofol administration, the higher the amount of propofol that may be necessary for induction.

The mean propofol induction doses with the remaining premedication regimens were consistent with the recommended protocol doses. Based upon these data and results from previous clinical studies, ranges for propofol induction with various premedications in a clinical environment have been established (see the Induction Dosage Guidelines table).

PROPOFOL MAINTENANCE ANESTHESIA:

An induction dose of propofol provided anesthesia for 4:32 to 10:30 (min:sec), depending on the anesthetic regime. An incremental or maintenance dose of propofol provided anesthesia for 3:55 to 7:23, varying according to premedicant.

A comparison of the mean induction dose intervals (min:sec) and mean induction doses (mg/kg) with the mean duration of anesthesia and doses for all maintenance intervals is shown in the following table:

Induction Regimen	**Induction Anesthetic Duration (min:sec)** **Mean Induction Dose (mg/kg)** **n**	**Mean Duration for Maintenance Intervals Only** **Mean Dose (mg/kg)** **n**
Propofol Only	6:52 6.47 40	6:26 1.48 48
Acepromazine/ Propofol	5:38 4.23 22	3:55 1.21 49
Oxymorphone/ Propofol	6:49 3.35 21	6:11 1.12 48
Xylazine/ Propofol	10:30 2.50 19	7:23 1.03 23
Butorphanol/ Propofol	4:34 4.49 9	4:14 1.45 11
Acepromazine/ Butorphanol/ Propofol	4:32 2.11 7	6:43 1.02 11

The mean propofol maintenance doses were consistent with the recommended label doses for propofol as used with premedicants (1.1 mg/kg), except for butorphanol. Butorphanol required 1.45 mg/kg of propofol (see maintenance induction guideline table under dosage and administration above).

Mean maintenance doses for propofol alone were 1.48 mg/kg, within the label recommended maintenance dose range of 1.1 to 3.3 mg/kg.

Maintaining surgical depth of anesthesia and avoiding the first plane of arousal during propofol maintenance anesthesia requires close attention. Several dogs showed signs of rapid anesthetic arousal. One investigator attempted a spay with propofol only, but depth of anesthesia was not sufficiently stable for the procedure and the dog was switched to an inhalant. However, several castrations were accomplished with propofol induction and maintenance only.

ANESTHESIA WITH PROPOFOL INDUCTION AND INHALANT MAINTENANCE:

As expected, the longest anesthetic episodes were maintained with inhalants rather than with propofol. Dogs were maintained with either isoflurane or halothane by changing vaporizer settings as necessary.

Instances occurred when the anesthetic duration following the induction dose of propofol was insufficient to complete transition to the inhalant. It may be necessary to increase initial vaporizer settings above those used with other induction anesthetics, in order to counterbalance the rapid recovery from propofol. Another alternative is to deliver a low maintenance dose of propofol. Several investigators administered small incremental doses of propofol during inhalant maintenance to rapidly deepen the plane of anesthesia, in addition to increasing vaporizer settings, resulting in two incidences of apnea. Apnea may also occur following a maintenance dose of propofol alone.

OVERALL ANESTHETIC EFFECTIVENESS:

Lists of the anesthetic effectiveness scores, and the mean and ranges of duration of anesthesia for all subregimens in the study are presented in the following table. Anesthetic effectiveness was subjectively scored as follows:

Excellent (E) = very good muscle relaxation, anesthesia completely adequate for procedure

Good (G) = not totally relaxed, but anesthesia sufficient for procedure

Fair (F) = unable to get good muscle relaxation, stayed light throughout procedure

Poor (P) = insufficient anesthesia for procedure

Regimen	Anesthetic Effectiveness Scores				Percent with Scores of Excellent or Good
	E	G	F	P	
Propofol Only	29	10	3		93% (39 of 42)
Propofol/acepromazine, no maintenance	8	1			100% (9 of 9)
Propofol/acepromazine, propofol maintenance	5	7	2		85% (12 of 14)
Propofol/acepromazine, halothane maintenance	9	3			100% (12 of 12)
Propofol/acepromazine, isoflurane maintenance	11				100% (11 of 11)
Propofol/oxymorphone, no maintenance	5	4	1		90% (9 of 10)
Propofol/oxymorphone, propofol maintenance	11		1		92% (11 of 12)
Propofol/oxymorphone, halothane maintenance	11	2			100% (13 of 13)
Propofol/oxymorphone, isoflurane maintenance	11	2			100% (13 of 13)
Propofol/xylazine, no maintenance	9	1			100% (10 of 10)
Propofol/xylazine, propofol maintenance	8	2			100% (10 of 10)
Propofol/xylazine, halothane maintenance	8		1		89% (8 of 9)
Propofol/xylazine, isoflurane maintenance	9	2			100% (11 of 11)
Propofol/butorphanol, no or propofol maintenance	5	3	1		89% (8 of 9)
Propofol/butorphanol, halothane maintenance	7	2			100% (9 of 9)
Propofol/butorphanol, isoflurane maintenance	5				100% (5 of 5)
Propofol/butorphanol/ acepromazine, no or propofol maintenance	5	2			100% (7 of 7)
Propofol/butorphanol/ acepromazine, halothane maintenance	6	2		1	89% (8 of 9)
Propofol/butorphanol/ acepromazine, isoflurane maintenance	6				100% (6 of 6)
Propofol only, Halothane maintenance	36	11	3	1	92% (47 of 51)
Propofol only, Isoflurane maintenance	41	6	1		98% (47 of 48)

RECOVERY:

The following table shows the mean times and ranges from the end of anesthesia to head lift, sternal recumbency, and standing, along with recovery scores.

Recovery was subjectively scored as follows:

Excellent = completely smooth recovery
Good = smooth recovery with minor paddling or tremors
Fair = paddling, thrashing when moving, sensitive to noise
Poor = rough recovery, vocalization, opisthotonus, clonic/tonic seizures

Means and ranges for head lift, sternal and standing intervals (hr:min:sec), and recovery comments are listed by drug regimens. Regimens are divided by either propofol, halothane, or isoflurane maintenance.

Regimen	**Head Lift Mean** **Range**	**Sternal Mean** **Range**	**Standing Mean** **Range**	**Recovery Comments** **E G F P**
Propofol Only	3:38 0:00-13:16	5:27 0:00-25:10	15:41 1:17-1:43:48	29 10 2 1
Propofol, halothane maintenance	3:02 0:00-12:06	6:08 0:00-27:08	16:00 3:12-43:13	34 11 4 1
Propofol, isoflurane maintenance	2:06 0:00-19:19	3:10 0:00-31:53	10:59 0:03-1:11:38	36 10 2
Propofol/ acepromazine, propofol or no maintenance	5:25 0:13-39:04	8:57 0:29-1:02:40	17:03 2:40-1:15:17	16 4 2 1
Propofol/ acepromazine, halothane maintenance	7:14 0:00-28:53	16:15 0:43-1:08:25	27:12 4:00-1:08:25	10 2
Propofol/ acepromazine, isoflurane maintenance	2:52 0:12-5:04	4:31 1:20-10:52	16:06 6:38-33:57	7 4
Propofol/ oxymorphone, no or propofol maintenance	1:38 0:00-9:11	2:56 0:01-10:35	9:27 0:28-16:02	19 1 1 1
Propofol/ oxymorphone, halothane maintenance	7:49 0:00-35:16	11:26 0:00-38:36	24:17 1:40-1:22:08	8 2 2

Regimen	Head Lift Mean Range	Sternal Mean Range	Standing Mean Range	Recovery Comments E G F P
Propofol/ oxymorphone, isoflurane maintenance	2:02 0:00-10:59	6:02 0:00-31:22	16:17 0:22-31:22	11 2
Propofol/ xylazine, no or propofol maintenance	5:59 0:00-18:39	6:48 0:20-18:51	12:27 1:15-35:19	18 2
Propofol/ xylazine, halothane maintenance	9:53 0:00-53:18	10:30 0:00-53:18	15:34 0:00-53:18	9
Propofol/ xylazine, isoflurane maintenance	4:07 0:00-14:42	5:21 0:00-19:07	12:40 1:09-52:05	8 2
Propofol/ butorphanol, no or propofol maintenance	3:47 0:00-13:52	6:10 1:27-17:49	11:27 2:00-24:00	8 1
Propofol/ butorphanol, halothane maintenance	4:13 0:00-9:55	17:28 0:00-1:44:06	37:42 7:37-1:58:16	7 2
Propofol/ butorphanol, isoflurane maintenance	1:44 0:52-2:58	4:04 1:12-8:16	11:03 6:25-15:41	2 2 1
Propofol/ butorphanol/ acepromazine, no or propofol maintenance	4:20 1:10-8:16	9:25 4:14-20:01	19:29 7:10-36:29	7
Propofol/ butorphanol/ acepromazine, halothane maintenance	5:05 0:00-15:36	10:07 0:00-20:53	1:54:55 6:20-7:12:55	6 3
Propofol/ butorphanol, acepromazine, isoflurane maintenance	3:59 0:53-10:45	9:19 2:03-17:41	26:56 7:43-59:38	2 4

93% (114 of 123) of dogs that received propofol for maintenance were classified as excellent or good recoveries. 95% of dogs (184 of 194) of dogs maintained with inhalants were classified as excellent or good.

Dogs that received repeated doses of propofol for maintenance anesthesia did not have increased recovery times indicating that the effects of propofol were not cumulative. Dogs that received repeated propofol maintenance doses had similar recovery times (15:43) compared to those receiving a single dose (12:21), also indicating that the effects of propofol were not cumulative.

Some dogs that received acepromazine/butorphanol premedication experienced profound sedation prior to propofol induction (9 of 24). Prolonged, sluggish recoveries resulted as well in some dogs that received this premedication regimen (see table above). It is recommended when using this regimen, that the dosage of one or more of the products (acepromazine, butorphanol, or propofol) may be further reduced to lessen pre-anesthesia sedation or prolonged recovery.

PHYSIOLOGICAL PARAMETERS:

Pulse Rate and Respiratory Rate:

The following table compares the physical exam, pre-induction, induction, and pre-procedure mean pulse rate (PR) and respiratory rate (RR) for each induction regimen. Mean values were only calculated when PR or RR were recorded for all four time periods (some measurements were not recorded accidentally or because of time constraints). For purposes of calculation, 60 breaths per minute were assigned to dogs that were noted to be panting.

Induction Regimen PR, RR (n,n)	**Physical Examination**		**Pre-induction**		**Induction**		**Pre-procedure**	
	PR	**RR**	**PR**	**RR**	**PR**	**RR**	**PR**	**RR**
Propofol Only (98,90)	113	44	129	43	133	26	130	26
Propofol Acepromazine (41,41)	125	44	124	28	122	18	118	23
Propofol Oxymorphone (44,41)	111	42	114	60	111	31	104	30
Propofol Xylazine (40,40)	109	41	80	25	81	20	84	19
Propofol Butorphanol (20,20)	116	39	111	37	122	31	116	34
Propofol Butorphanol/ acepromazine (20,20)	114	39	97	25	105	24	94	27

PR:

Mean PR were variable depending on the premedicant. PR decreased in the xylazine and ace/butorphanol groups during the preinduction period. Oxymorphone, acepromazine, and butorphanol caused minimal changes in PR.

A transient increase in PR was seen after propofol induction when either butorphanol or ace/butorphanol were used for premedication. Following induction with propofol in the other premedication groups, minimal changes in PR were noted.

RR:

Premedicants during the preinduction period decreased RR in the ace, xylazine, and ace/butorphanol groups, caused minimal changes in the propofol only and butorphanol groups, and increased RR in the oxymorphone group.

On the whole, propofol induction caused RR to decrease in all groups; however, the decrease was minimal in the ace/butorphanol group.

Blood Pressure:

Measurements were taken at preinduction, induction, and preprocedure periods to determine the effect on BP of propofol alone or in conjunction with premedicants.

Systolic, diastolic, and mean BP were measured at one facility (MSU) in 22 dogs. The following table shows the mean values for the four test groups that were investigated at this facility. Butorphanol and ace/butorphanol were not investigated at this facility.

Induction Regimen	**n**	**Pre-induction Mean**			**Induction Mean**			**Pre-procedure Mean**		
		Sys	**Dia**	**Mean**	**Sys**	**Dia**	**Mean**	**Sys**	**Dia**	**Mean**
Propofol Only	5	159	76	86	137	89	102	129	81	89
Propofol Acepromazine	1	143	95	116	154	99	119	118	60	78
Propofol Oxymorphone	13	146	89	106	118	60	78	107	55	73
Propofol Xylazine	3	119	71	90	146	102	114	102	62	78
Range Minimum	22	105	53	59	96	50	61	82	43	56
Range Maximum	22	184	119	140	178	120	134	145	99	117

Systolic BP only was measured at two other sites (CSU & HEAC). The following table shows the mean systolic BP values for all the test groups evaluated at all three sites (MSU, CSU, HEAC):

Induction Regimen	**n**	**Pre-induction Mean Systolic Blood Pressure**	**Induction Mean Systolic Blood Pressure**	**Pre-procedure Mean Systolic Blood Pressure**
Propofol Only	7	148	142	128
Propofol Acepromazine	2	122	132	114
Propofol Oxymorphone	24	142	119	109
Propofol Xylazine	9	138	142	122
Propofol Butorphanol	2	120	117	120
Propofol Butorphanol/ acepromazine	5	102	107	102
Range Minimum	49	75	92	75
Range Maximum	49	200	201	190

BP results were variable depending on the premedicant. Prior to induction, BP increased with acepromazine and xylazine premedication, and decreased with propofol only or oxymorphone premedication. Systolic BP decreased for all regimens during the time period between induction and the start of the procedure.

Most of the mean BP in these tables are within acceptable clinical ranges. Systolic BP for a few dogs was outside the "normal" range (hypotensive or hypertensive). These dogs tolerated anesthesia without problems. The study raised no safety concerns regarding BP following the use of propofol for induction with and without premedicants.

OXYGEN SUPPLEMENTATION:

Dogs (n = 123) that received only an induction dose of propofol or propofol maintenance anesthesia received oxygen supplementation at the discretion of the investigator. Of these dogs, 82 were <u>not</u> supplemented with oxygen for propofol induction or induction/maintenance. These dogs breathed room air for short procedures and recovered normally while breathing room air. One of these dogs experienced apnea that resolved without administration of oxygen.

Although 82 cases were completed without administration of supplemental oxygen, the procedures were short and uncomplicated in primarily healthy dogs. Twenty-five dogs received a single dose of propofol. Conclusions cannot be drawn concerning the safety of using propofol without available oxygen supplementation. Therefore, the label contains "boxed" warning information stating that the use of propofol without available supplemental oxygen and artificial ventilation has not been adequately evaluated and is not recommended.

SIDE EFFECTS:

<u>Apnea:</u>
Induction apnea (within 10 minutes of induction) was the most common side effect of propofol administration (20%). The following table contains a comparison of cases of apnea by the various induction regimens.

Incidence of induction (I) and maintenance (M) apneas
and duration of apnea (mean and range; min:sec)

Regimen **N**	**Number of Apnea Observations (%)**	**Duration of Apnea** **Mean** **Range**
Propofol Only* 141	28 I (20%)	3:42 0:14 - 18:00
Propofol / Acepromazine 47	5 I 1 M (13%)	11:17 1:13 - 17:53
Propofol / Oxymorphone** 48	16 I 1 M (35%)	8:56 1:17-27:00
Propofol / Xylazine** 41	5 I 2 M (17%)	4:14 0:31-12:45
Propofol / Butorphanol 24	2 I (8%)	9:40 7:41-11:39
Propofol / Butorphanol / Acepromazine 24	4 I (17%)	9:09 1:00-27:48
Total - 325	60 I 4 M (20%)	

* 2 end of apnea times not recorded
** 1 end of apnea time not recorded

The incidence of apnea and the mean duration of apnea varied by premedicant regimen. Dogs given propofol alone or with xylazine premedication, had mean durations of apnea of approximately 4 minutes. Dogs which received the remaining premedication regimens had mean durations of apnea of approximately 9 - 11 minutes. In addition to propofol's depression of the respiratory center, the opioid premedicants (oxymorphone, butorphanol) affect the response to the presence of C02, as does the administration of oxygen (depression of respiration) and assisted ventilation (C02 washout depresses respiration). This may be the reason apnea was longer in duration for these premedicant treatment groups compared to propofol alone or with xylazine.

Propofol induction after oxymorphone premedication had the highest incidence of apnea (17/48; 35 %). Therefore, the total amount of propofol administered for induction after oxymorphone premedication was considered too high for some dogs. The induction dose for propofol should range from 2.2 mg/kg (1.0 mg/lb) to 3.3 mg/kg (1.5 mg/lb) to reduce the incidence of apnea, and this adjustment was made in the Induction Dosage Guidelines.

Two occurrences of apnea during maintenance with inhalant anesthesia were due to excess depth of anesthesia from high vaporizer settings and concurrent propofol incremental doses administered during inhalant anesthesia. The concurrent administration of propofol with a simultaneous increase in inhalant concentration is not recommended during maintenance anesthesia.

There were also two incidences of apnea following maintenance injections of propofol. Regardless of incidence or length, all apnea cases were managed with oxygen supplementation and assisted or controlled ventilation.

Side Effects Other Than Apnea:

1. Respiratory (n = 16; 4.9%, excluding apnea):

   reverse sneezing (n = 10)
   panting throughout procedure (n = 3)
   shallow, slow respirations throughout procedure (n = 1)
   non-productive cough during recovery (n = 1)
   brief, respiratory "rattle" during recovery (n =1)

2. Neurological (n = 18; 5.5%):

   excitation during induction (n = 3)
   excitation during recovery (n = 4)
   excitation throughout procedure (n = 1)
   opisthotonus (n = 4)
   nystagmus (n = 2)
   head tilt, circling (n = 1)
   petit mal seizure or seizure-like activity (n = 2)
   excessive depression (n = 1)

3. Musculoskeletal (n = 35; 10.8%):

   paddling during recovery (n = 20)
   paddling during maintenance (n = 1)
   tremors during induction (n = 3)
   tremors during maintenance (n = 3)
   tenseness (n = 3)
   foreleg movement (n = 2)
   fasciculations (n = 1)
   shivering during recovery (n = 1)

4. Gastrointestinal (n = 14; 4.3%):

   emesis/retching during procedure (n = 2)
   emesis/retching during recovery (n = 8)

salivation and/or drooling throughout procedure (n = 1)
salivation and/or drooling throughout recovery (n = 2)
defecation during recovery (n = 1)

5. Cardiovascular (n = 11; 3.4%):

tachycardia during induction (n = 1)
bradycardia (n = 8)
cyanosis (n = 1)
hypotension (n = 1)

6. Other (n = 24; 7.4%):

slow recovery (n = 11)
rubbing at face or nose during recovery (n = 5)
vocalization during recovery (n = 2)
extravascular pain (n = 3)
intravascular pain (n = 1)
chewing movement during intubation (n = 1)
response to noise (n = 1)

Some of the anesthetic side effects are not unique to propofol. Some side effects noted during recoveries from propofol were also noted for recoveries from the inhalants with similar incidence (propofol : inhalant), e.g., paddling (10:10), opisthotonus (3:1), nystagmus (1:1), and vocalization (1:1). These recovery side effects following propofol induction with inhalant maintenance are assumed not to be due to propofol since the duration of inhalant anesthesia exceeded the 23 minute mean duration that propofol alone provided anesthetic effect (means of 7 minutes anesthesia for propofol induction and 16 minutes from end of anesthesia to standing).
Side effects were, overall, transient and resolved on their own. Many anesthetic and physiological side effects noted during the field study were not unique to propofol but are also typically observed in any population receiving premedication to anesthesia and/or anesthesia regardless of the anesthetic agent.
One case of pain following intravascular injection was noted; three of 9 extravascular injections of propofol caused pain. Pain during propofol injection has been noted in other studies and in the literature.
One death (CVH, 7/20/95, #14622-B) occurred eight hours after anesthesia that was <u>not</u> attributed to anesthesia (propofol induction, halothane maintenance). The patient was an obese geriatric dog admitted for minor surgery (eyelid tumor, aural hematoma). The dog experienced a prolonged recovery, but died > five hours after recovery. Death was attributed to possible cardiac insufficiency by the pathologist.

Sighthounds:

During the course of the study eleven sight hounds (10 greyhounds and 1 Irish wolfhound) were anesthetized. These breeds have been reported to be more sensitive to anesthesia than other breeds.

Regimen	**Number**	**Apnea**
Propofol induction, isoflurane maintenance	9	0
Oxymorphone, propofol, halothane	1	1 (8'11")*
Butorphanol, propofol, halothane	1	0

*The recommended propofol dose for use with this premedicant has been reduced on the label from the dose used in the clinical trial.

Propofol was administered over 11 to 60 seconds. No side effects were noted except for one episode of apnea (propofol given over 60 seconds).

Anesthetic induction with propofol was satisfactory; however, all sighthounds were maintained with inhalant anesthetics. No conclusions can be drawn on the efficacy or safety of propofol as a maintenance anesthetic in sighthounds or on anesthetic recovery from propofol. However, in the literature, propofol anesthesia has been associated with longer recovery periods in sighthounds (see reference Robertson, et.al., 1992).

5. Target Animal Safety:

The safety of propofol was evaluated in three pivotal studies:

a. Acute Toxicity Studies in Beagles by Intravenous (IV) Administration.

b. Thirty day IV Toxicity Study in Dogs.

c. IV Tolerance Study in Dogs.

a. ACUTE TOXICITY STUDIES IN BEAGLES BY IV ADMINISTRATION:

Study Directors:
Dr. I. D. Cockshott, Mr. J P. Holland, Mr. P. G. Morrisey, Mr. P. J. Simons
Zeneca Pharmaceuticals (formerly Imperial Chemical Industries, PLC)
Mereside
Alderley Park
Macclesfield
Cheshire SK10 4TG, England

Dr. Michiko Aoki (Project Leader)
Dr. Kiyoshi Imai (Study Director)
Food and Drug Safety Center
Hatano Research Institute
729-5 Ochiai
Hatano
Kanagawa 25, Japan

The acute toxicity study was conducted for ICI Pharmaceuticals Manufacturing Ltd. by the Food and Drug Safety Center at Hatano Research Institute in Japan. The study was conducted in compliance with Japanese GLP Standards for Safety Studies on Drugs. Study dates ranged from arrival date October 16, to dosing dates November 26 and December 3, 1990.

Preliminary findings:

To determine test groups for this study, two dogs were given propofol. 10 mg/kg was given to one male at 0.5 mg/sec. The dog was anesthetized and recovered after 30 minutes. A second male was given 20 mg/kg. After 14 minutes of anesthesia, the dog died.

Acute Toxicity Study Design:

Dose Groups:
Four beagle dogs (2 male, 2 female/9-10 months) were chosen for each of the following 3 groups:
20 mg/kg (2 mL/kg) = 3X
30 mg/kg (3 mL/kg) = 4.5X
40 mg/kg (4 mL/kg) = 6X

A single injection of propofol was administered into the cephalic vein at 0.5 mg/sec. The dogs were observed for 14 days following the injection. Gross necropsy only was done immediately on any animal that died.
Results:
The dogs in the 20 mg/kg group were dosed first; when none died, four more dogs were given 40 mg/kg. When all four of those dogs died within one minute after the end of propofol administration, the 30 mg/kg group was added to the study. One female at 30 mg/kg died shortly after dosing. All other animals were anesthetized; recovery occurred within 45-60 minutes (30 mg/kg dose) or 20-30 minutes (20 mg/kg dose) after dosing. Over the following 14 days, no adverse effects were noted in the surviving dogs.

The following table provides clinical signs recorded for each dog during the study, including the times during anesthesia when the signs were observed. Times are shown as minutes after starting administration of propofol (given at 0.05 mL/sec):

Dog	**Dose mg/ kg**	**Cyanosis**	**Mydriasis**	**Cessation Respiration**	**Cardiac Arrest/ DEATH**	**Complete Recovery**
1	20	8-12 min	8-10	-	-	60
2	20	-	-	-	-	60
7	20	-	-	-	-	50
8	20	-	-	-	-	50
5	30	7-15	-	-	-	50
6	30	6-10	9-10	9-10	10	-
11	30	-	-	-	-	50
12	30	15-16	-	-	-	60
3	40	4-14	7-14	12-14	14	-
4	40	11-12	11-12	12	12	-
9	40	14-16	14-16	15-16	16	-
10	40	12-16	15-16	15-16	16	-

The table shows the progression of clinical signs associated with propofol overdose when dogs are spontaneously breathing room air. These signs are not unique to this anesthetic. Cyanosis and mydriasis are relatively early signs of excessive anesthesia that serve as an indication that supplemental oxygen is necessary.

Gross necropsy findings were not specifically pathological for propofol:

cyanotic oral mucous membranes (all dead dogs)
hepatic congestion (all 40 mg/kg animals)
renal cortical congestion (3 dogs in the 40 mg/kg group)
pulmonary effusion (1 dog in the 40 mg/kg group)
congestion in lung and GI tract (1 dog in the 30 mg/kg group)
splenic congestion (1 dog: 30 mg/kg/ 3 dogs: 40 mg/kg)

Conclusion:

The administration of propofol without respiratory support (oxygen supplementation, ventilation) may be lethal or result in severe respiratory depression at doses equivalent to 3X or greater (>20 mg/kg) than the recommended induction dose.

b. THIRTY DAY IV TOXICITY STUDY IN DOGS:

Study Directors:
Dr. I. D. Cockshott, Mr. J P. Holland, Mr. P. G. Morrisey, Mr. P. J. Simons
Zeneca Pharmaceuticals (formerly Imperial Chemical Industries, PLC)
Mereside
Alderley Park
Macclesfield
Cheshire SK10 4TG, England

The objective of the study was to determine the toxicity of repeated intravenous doses of propofol in the dog over a 30 day period. The study was conducted in the United Kingdom in 1982 using GLP's.

Test Groups:

Ten dogs (5 female and 5 male) were used in each of the following groups:

Group I = saline control (1 mL/kg)
Group II = vehicle control (1 mL/kg)
Group III = 5 mg/kg (0.76X) propofol bolus (0.5 mL/kg)
Group IV = 10 mg/kg (1.5X) propofol bolus (1.0 mL/kg)
Group V = 30 mg/kg/day (total of 4.5 X)

Groups I through IV were dosed daily for 30 days before feeding.

For Group V dogs, the entire dose of 30 mg/kg was drawn into a syringe. After the induction dose was given (7.5 mg/kg) the remainder of the dose was infused at a rate of 0.05 mL/kg/minute using an injection pump. The animals in Group V were dosed three times per week during the four week study (total of 13 times).

Prior to inclusion in the study, selected dogs had all given acceptable results in a complete physical examination, including hematology and serum chemistry.

Final selection and allocation to dose groups took place at least 25 days before the first dose. The study was staggered on a replicate basis. Necropsy took place on day 31 of the study.

Test Article:

Propofol (10 mg/mL) was administered to Groups I-IV with a sterile syringe and a 20 gauge, 1 inch needle. The left and right cephalic veins were used on alternate days. Group V dogs were dosed with a sterile syringe and a butterfly needle connected to an infusion pump. The injection was given in the left or right saphenous vein.

Rate of Administration:

The intended injection times for Groups I, II, and III were 30 seconds. Group IV injection time was changed from 90 seconds to 60 seconds to avoid problems associated with slower induction such as struggling. The injection times were recorded only if greater or less than 5 seconds of the intended time.

Group V received the induction dose over 60 seconds, and the subsequent infusion over 45 minutes (range 40-55 minutes).

Observations and Measurements:

Physical Examination:

Each dog was given a full veterinary examination at least once prior to the study and during
weeks 2 and 4 during the study. Dogs were also assessed twice daily and any abnormalities
were recorded.

Daily observations and veterinary examination did not demonstrate any effects due to propofol administration. No dogs became ill or died during the study.

Body Weight:

Individual body weights were recorded twice weekly for two weeks prior to the study and throughout the study. Body weight and body weight gain were unaffected by the administration of propofol.

Food Consumption:

Every day each dog was offered 400 gm of the laboratory diet at approximately the same time. Any remaining food was removed the following morning, the weight was estimated and recorded as a percentage of the amount that was offered. The records begin two weeks before the study until the study ended.

The food consumption of some dogs from all groups, including controls, was lower than normal at times, especially during the second half of the study. Effects on food consumption were not specifically attributable to propofol.

Recovery Time:

The time from the end of dose administration to recovery of consciousness was recorded:

a. twice during the first week of dosing

b. once during the second week of dosing

c. once during the third week of dosing

d. twice during the fourth week of dosing

The following table represents the group mean values for recovery times in minutes:

	Group III	**Group IV**	**Group V**
Firt dose	5.70	11.20	9.80
Last dose	8.40	25.56	18.15
Difference	2.70	14.24	8.35

The recovery times were dose-related for the daily injection groups (III and IV). The infusion group (30 mg/kg/day) did not remain anesthetized as long as the 10 mg/kg dose group (IV).

As the study progressed, the recovery times lengthened for dogs from Groups III, IV, and V. This increase was statistically significant for Groups IV and V ($p<0.01$).

A concurrent pharmacokinetic drug withdrawal test was conducted with separate groups of dogs (Cockshott, 1983). Drug withdrawal animals (3 males and 3 females) were added to Groups I, II, and V, and were treated the same as the main test dogs throughout the 30 day dosing period. These dogs were not necropsied, and remained under observation for another 6 weeks. The area under the propofol blood concentration curve for Groups III and IV was not statistically different between the first dose and the last dose. This indicates that propofol did not accumulate with daily administration over 30 days at the same doses that were used in the safety study. Therefore, the increase in recovery times seen with repeated doses is probably not due to drug accumulation.

Physiological parameters:

Physiological parameters were measured on all dogs in Groups I, IV, and V once prior to the study, once during week 2 and once during week 4. The occurrence of apnea was not recorded. The following measurements were made predose and approximately 3 hours after the dose:

HR, RR, T°
ECG
Direct arterial blood pressure (BP)

No physiological differences between the control groups and the dosed groups were considered to be toxicologically important or related to the administration of propofol.

Hematology and Serum Chemistry:

Blood was collected before dosing from the jugular veins of all animals at the following times:

a. twice before the study

b. once during week 2

c. once during week 4

Hematology included the following:

PCV	Total WBC count
Hb	Differential WBC count
RBC count	Platelet count
Mean RBC volume	
Mean RBC Hb	Prothrombin time
Mean RBC Hb conc.	Partial thromboplastin
RBC metHb (4 wk only)	time

None of the differences between controls and any dosed group mean results were considered of toxicological importance.

The group mean PTT was significantly lower in Group III dogs during the second week of dosing. It was not considered to be of toxicological importance.

Serum Chemistry included the following:

glucose	AST
total protein	ALT
albumin	AP
total bilirubin	CK
BUN	

No serum chemistry changes were considered to be of toxicological importance.

Urinalysis (UA):

Urine was collected by catheterization for cytology and analysis from all animals in Groups I and IV at the following times:

a. once prestudy

b. once prior to first dosing

c. once during week 2

d. once during week 4

Measurements included the following:

volume	protein
cytology	blood
bilirubin	pH
ketones	specific gravity
glucose	color

None of the changes in the urinary parameters were considered to be of toxicological importance.

Pathology:

Dogs were humanely killed on the day following the final dose. A complete necropsy was done on all dogs and satisfactory tissue samples were collected for histopathology.

Organ weights were taken on adrenal glands, brain, epididymides, heart, kidneys, liver, ovaries, pituitary, testes, and thyroid glands.

At necropsy, there were no changes in organ weights or any macroscopic or microscopic tissue changes that were attributed to propofol.

This study supports the safe use of propofol for induction of anesthesia in dogs.

c. INTRAVENOUS INJECTION SITE STUDY:

Study Directors:
Dr. I. D. Cockshott, Mr. J P. Holland, Mr. P. G. Morrisey, Mr. P. J. Simons
Zeneca Pharmaceuticals (formerly Imperial Chemical Industries, PLC)
Mereside
Alderley Park
Macclesfield
Cheshire SK10 4TG, England

Objective:

The study was designed to examine the tolerance of the cephalic vein wall to the intravenous injection of propofol. The study was conducted under GLPs (study dates November 16-18, 1982). Propofol (10 mg/mL) was formulated and tested to the same specifications as the sales formulation.

Test Animals:

Two male and two female beagles (11-16 months old; 12.9-16.4 kg) were acclimated for a week in satisfactory housing.

Study Design:

Each dog received an injection of a control product (sterile saline) into the right cephalic vein and an injection of propofol into the left cephalic vein on three consecutive days. The dose was 10 mg/kg (1.5X). The dose volume for the control and test article was 1 mL/kg, administered at the rate of approximately 1.2 mL/sec (approx. 15 sec).

Injections were made using a 25mm X 20 gauge needle. The study did not evaluate pain on injection.

Injection areas were examined immediately before and after injection, approximately 1, 2, and 6 hours after injection on days 1 and 2, and 1 and 2 hours after injection on day 3.

Following humane euthanasia on day 3, approximately 8 cm of cephalic vein was removed from each leg and the following specimens were removed:

Site A	1.5 cm, centered 3 cm proximal to the injection site (direction of blood flow).
Site B	1.5 cm, centered 6 cm proximal to the injection site.

All these specimens were examined histopathologically, except for the right cephalic (control) of one dog (#37102).

Results:

In two dogs, small volumes of propofol, and in one animal the saline control, were injected subcutaneously on day one. A second, more proximal injection site was used in these dogs. No other abnormal observations were noted.

Necropsy:

Gross: Hemorrhage or blood clot was seen at all injection sites as a result of repeated venipuncture. This was not associated with the administration of propofol since hemorrhage was noted in both legs (control and propofol).

Histopathology: No abnormalities were seen in the walls of the veins examined.

The study satisfactorily examines the potential for tissue irritation at the injection site. Propofol did not produce local irritation when injected into the cephalic vein.

6. Supportive Studies:

a. Sighthounds:

1) Robertson, et al. (1992) determined the cardiopulmonary, anesthetic, and postanesthetic effects of intravenous infusions of propofol in Greyhounds (n = 6) and non-Greyhounds (n = 7). Dogs were premedicated with atropine and acepromazine, anesthesia was induced with propofol (4.0 mg/kg in greyhounds, 3.2 mg/kg in non-greyhounds), then maintained by infusion at 0.4 mg/kg/minute. Recovery was approximately 30 minutes slower in Greyhounds.

2) Zoran, et al. (1993) compared the pharmacokinetics of propofol using 8 mixed-breed dogs and 10 greyhounds. Anesthesia was induced with 5 mg/kg of propofol, with additional drug given if needed for intubation. Disposition of propofol was adequately described by a two-compartment model. Greyhounds had higher propofol levels in plasma, a lower volume of distribution, slower total body clearance rates, and longer recovery times than did mixed-breed dogs. The

elimination half-life was similar in both groups. This report confirmed that recovery may be slower in greyhounds, and provided an explanation based upon differences in pharmacokinetics.

3) Mandsager, et al. (1993) determined the effects of chloramphenicol on the pharmacokinetics of propofol in greyhound dogs. Thirty minutes prior to anesthesia, two groups of 5 dogs each were given intravenous doses of either saline or chloramphenicol (50 mg/kg). All dogs were induced with 10 mg/kg of propofol and maintained by infusion at 0.4 mg/kg/minute. Chloramphenicol (a cytochrome P-450 inhibitor) increased the half life of propofol by 209 %, decreased body clearance by 45 %, and prolonged recovery by 768 - 946 %. This report shows that other medications may alter the pharmacokinetics of propofol.

b. Arrhythmogenicity:

Kamibayashi, et al. (1991) determined the effects of propofol on epinephrine-induced arrhythmias in dogs. They used 62 dogs anesthetized with propofol (N = 8; 10 mg/kg bolus followed by 40 mg/kg/hr infusion), halothane (N = 8), etomidate (N = 8), etomidate/ alcuronium (N = 8), etomidate/alcuronium plus propofol infusion (5, 10, or 20 mg/kg/hr; N = 8, 7, and 7, respectively), and etomidate plus propofol vehicle (N = 8). Epinephrine was infused at 60 minutes after the start of anesthesia. Propofol enhances epinephrine-induced arrhythmias in a dose-dependent manner, similar to several other anesthetic agents (for example, thiopental and halothane).

c. Propofol Pharmacokinetics:

1) Cockshott (1983) performed HPLC analyses of plasma samples from dogs during the pharmacokinetic drug withdrawal test that was conducted with the main target animal safety study (Morrisey, 1983). The pharmacokinetics fitted a two compartment open model. Following bolus doses of 5 or 10 mg/kg, propofol was rapidly distributed into a large apparent volume of distribution (81 L). Propofol clearance was characterized by an elimination half-life of 27 minutes. After an induction dose followed by maintenance infusion, steady state propofol plasma concentrations were achieved within 25 minutes of the start of the infusion. The mean concentration at steady state was 6.2 μg/mL. The elimination half life was 35 minutes.

2) Cockshott et al. (1992) published a second study which also involved single doses or induction doses followed by infusion. In the first part of the study, 3 dogs were given 7 mg/kg of propofol. Two weeks later, they were dosed with 7 mg/kg followed by infusion at 0.47 mg/kg/min for 6 hours. In the second part of the study, 8 male and 8 female dogs were induced with 7.5 mg/kg followed by infusion of 0.5 mg/kg/min for 4 hours, four times within 2 weeks. The pharmacokinetics of propofol were best described by a three compartment model. Following a single injection, there was a large initial volume of distribution (1.4 L/kg), and extensive redistribution (11.4 L/kg). The total body clearance was rapid (76 mL/kg/min). After the infusion dose, the volume of distribution (1.0 L/kg) was similar, but the redistribution compartment was less (6.6 L/kg). The total body clearance rate was slower (34 mL/kg/min).

d. Propofol Metabolism:

1) Simons (1983) administered ^{14}C propofol to 3 male and 3 female dogs. The dose given was 9.7 mg/kg. The excreta were collected, and plasma samples were collected through 120 hours after dosing. Recovery was approximately 60 % in the urine and 29 % in the feces. Urine metabolites included glucuronic acid (24 %) and sulfate (22 %) conjugates of 2,6 di-isopropyl 1,4 quinone. The feces contained 2,6 di-isopropyl 1,4 quinone (4 %) and polar metabolites which were not identified. The apparent elimination half-life of propofol from plasma was approximately 24 minutes.

2) Simons et al. (1991) published the results of a second study which included both induction and induction plus maintenance. Male dogs (N = 3) were given a single propofol dose of 7.2 mg/kg. One month later, they were dosed with 7.3 mg/kg followed by infusion at 0.47 mg/kg/min for 6 hours. Elimination was approximately 70 % in urine and 30 % in feces, and was similar for single doses and infusion administration. Propofol metabolism shifted during the 6 hours of infusion, from the sulfate conjugates to more glucuronic acid conjugates.

e. Effects of propofol on pharmacokinetics and metabolism of propanolol:

Perry et al. (1991) determined the effect of propofol on drug distribution and metabolism of propanolol. On the first of two successive days, the procedure was performed in 6 awake dogs. On the second day, anesthesia was induced with 8 mg/kg and maintained with 0.8 mg/kg/minute of propofol. Propofol reduced intrinsic clearance of propanolol by 40 %, increased the volume of distribution, and increased the free-fraction (non-protein bound) of propanolol. These results show that propofol may have effects on the pharmacokinetics or metabolism of other drugs administered to dogs.

7. Human User Safety:

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of the NADA. This 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).

8. Agency Conclusions:

The data in support of this NADA comply with the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act and Section 514.111 of the implementing regulations. It demonstrates that Rapinovet® (propofol) Anesthetic Injection, when used under labeled conditions of use, is safe and effective.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is judged to be critical in the administration of a drug that provides induction and maintenance of general anesthesia. If the product is used without the knowledge necessary for understanding the physiological effects of propofol and its potential interactions with other drugs commonly used before and/or during

general anesthesia, the efficacy of the drug may change, and the safety of the animal could be jeopardized.

Under Section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for five years of marketing exclusivity beginning on the date of approval because no active ingredient (including any ester or salt of the active ingredient) of the drug, has been approved in any other application.

9. References:

Aoki, M. and Imai, K. 1995. ICI 35,868 - Acute toxicity study in Beagles by intravenous administration. Hatano Research Institute Research Report HRI 2-911.

Cockshott, I. D. 1983. 'Diprivan' (ICI 35,868): Pharmacokinetics in the dog after single and multiple administrations of the emulsion formulation (Study Number TAD/305). Imperial Chemical Industries Research Report 5/HC/005608.

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

Holland, J. P. 1983. 'Diprivan' (ICI 35,868) intravenous tolerance study in dogs (Study Number TID/304). Imperial Chemical Industries Research Report 5/HC/005607.

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

Mandsager, R. E., C. R. Clarke and R. V. Shawley. 1993. The effects of chloramphenicol on the pharmacokinetics of propofol in greyhound dogs. Vet. Surg. 23:76 (Abstract).

Morrisey, P. G. 1983. 'Diprivan' (ICI 35,868): 30 day intravenous toxicity study in dogs (Study Number TAD/305). Imperial Chemical Industries Research Report 5/HC/005581.

Perry, S. M., E. Whelan, S. Shay, A. J. J. Wood and M. Wood. 1991. Effect of intravenous anaesthesia with propofol on drug distribution and metabolism in the dog. Br. J. Anaesth. 66:66-72.

Peterson, K. D. 1995. Clinical trial under field conditions with propofol (2,6 diisopropylphenol; 1% w/v) in dogs. Mallinckrodt Veterinary Research Report P210-004-R.

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

Short, C. E. and Campbell, D. G. 1995. Compatibility of propofol in dogs when used in combination with pre-anesthetics and inhalant anesthetics. Mallinckrodt Veterinary Research Report P210-010-R.

Short, C. E. and Salsbury, D. L. 1994a. Propofol (2,6 diisopropylphenol) dose determination study (Phase 1) in dogs. Mallinckrodt Veterinary Research Report P210-007-R.

Short, C. E. and Salsbury, D. L. 1994b. Propofol (2,6 diisopropylphenol) dose determination study (Phase 2) in dogs. Mallinckrodt Veterinary Research Report P210-008-R.

Simons, P. J. 1983. 'Diprivan' (ICI 35,868): A study of metabolism, blood levels, and elimination following intravenous administration of ^{14}C-ICI 35,868 at 10 mg/kg to male and female dogs (emulsion formulation) (Study Number ICI 35,868/PJS/10). Imperial Chemical Industries Research Report 5/HC/005614.

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

Thurmon, J. C., W. J. Tranquilli and G. J. Benson, eds. 1996. Preanesthetics and anesthetic adjuncts. Chapter 8 in: Lumb and Jones' Veterinary Anesthesiology, 3rd Ed.

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

10. Labeling (attached):

Package Insert
Ampule Label
Carton Label

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.