Date of Approval: September 6, 2012

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-342

ALFAXAN

Alfaxalone
10 mg/mL Intravenous injectable anesthetic
Cats and Dogs

ALFAXAN is indicated for the induction and maintenance of anesthesia and for induction of anesthesia followed by maintenance with an inhalant anesthetic, in cats and dogs.

Sponsored by:

Jurox Pty. Ltd.

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I. GENERAL INFORMATION:

A. File Number:	NADA 141-342
B. Sponsor:	Jurox Pty. Ltd. 85 Gardiner Rd. Rutherford, NSW 2320 Australia Drug Labeler Code: 049480 U.S. Agent: James H. Schafer, D.V.M. Schafer Veterinary Consultants, LLC 800 Helena Court Fort Collins, CO 80524
C. Proprietary Name:	ALFAXAN
D. Established Name:	Alfaxalone
E. Pharmacological Category:	Anesthetic
F. Dosage Form:	Injectable
G. Amount of Active Ingredients:	10 mg/mL
H. How Supplied:	10 mL single use vials
I. How Dispensed:	Rx
J. Dosages:	See below
K. Routes of Administration:	Intravenous
L. Species/Classes:	Cats and Dogs
M. Indications:	ALFAXAN is indicated for the induction and maintenance of anesthesia and for induction of anesthesia followed by maintenance with an inhalant anesthetic, in cats and dogs.

J. Dosages:

CAT DOSAGE

Induction of general anesthesia in cats: Induction dose guidelines are based on data from the field study (see EFFECTIVENESS) and range between 2.2 - 9.7 mg/kg for cats that did not receive a preanesthetic, and between 1.0 - 10.8 mg/kg for cats that received a preanesthetic. The ALFAXAN induction dose in the field study was reduced by 10-43%, depending on the combination of preanesthetics (dose sparing effect). To avoid anesthetic overdose, titrate the administration of ALFAXAN against the response of the patient. Dose sparing of ALFAXAN will depend on the potency, dose, and time of administration of the various preanesthetics that are used prior to induction. To avoid anesthetic overdose, titrate the administration of ALFAXAN against the response of the patient.

Anesthesia is usually observed within 60 seconds after the start of injection, and permits intubation within 1 - 2 minutes, irrespective of preanesthetic. The duration of anesthesia from a single induction dose ranges between 15 - 30 minutes in the unpreanesthetized cat. If a preanesthetic is used, anesthetic duration may be longer, depending on the class and dose of preanesthetic. Individual anesthesia times vary.

Examples from the field study of average induction doses (and ranges) for cats that received various preanesthetics are presented as dosing guidelines in the table. The table is for guidance only. The actual induction dose should be based on patient response.

Table 1: ALFAXAN Induction Dose Guidelines: CATS

Preanesthetic	Average ALFAXAN induction dose (and range) in mg/kg	Number of cats
No preanesthetic	4.0 (2.2-9.7)	33
Opioid + phenothiazine	3.2 (1.1-10.8)	96
Benzodiazepine + opioid + phenothiazine	2.3 (1.2-5.0)	26
Benzodiazepine + phenothiazine	3.6 (1.5 – 7.1)	23
Alpha$_2$-adrenergic agonist with/without phenothiazine	3.6 (1.1-5.0)	15
Alpha2-adrenergic agonist + phenothiazine with/without benzodiazepine or opioid	2.9 (1.0-3.9)	11

Additional doses of ALFAXAN similar to those used for maintenance (1.1 - 1.5 mg/kg) may be administered to facilitate intubation.

Maintenance of general anesthesia in cats: Following induction of anesthesia with ALFAXAN and intubation, anesthesia may be maintained using intermittent ALFAXAN intravenous (IV) boluses or an inhalant anesthetic agent. A maintenance bolus containing 1.1 – 1.3 mg/kg provides an additional 7 - 8 minutes of anesthesia in preanesthetized cats. A dose of 1.4 - 1.5 mg/kg provides an additional 3 - 5 minutes anesthesia in unpreanesthetized cats. Clinical response may vary, and is determined by the dose, rate of administration, and frequency of maintenance injections.

ALFAXAN maintenance dose sparing is greater in cats that receive a preanesthetic. Examples from the field study of maintenance doses for preanesthetized and unpreanesthetized cats are presented as guidelines in the table. Maintenance dose and frequency should be based on the response of the individual patient.

Table 2: ALFAXAN Maintenance Dose Guidelines: CATS

Dose and Duration	Preanesthetized cats	Unpreanesthetized cats
Maintenance anesthesia doses	1.1 – 1.3 mg/kg	1.4 – 1.5 mg/kg
Mean duration of anesthesia	7 – 8 minutes	3 – 5 minutes

In the field study, recovery times (extubation to head lift) following ALFAXAN maintenance anesthesia averaged 15 minutes in cats that did not receive a preanesthetic, and 17 minutes in preanesthetized cats.

Inhalant anesthetic maintenance of general anesthesia in cats: Additional low doses of ALFAXAN, similar to a maintenance dose, may be required to facilitate the transition to inhalant maintenance anesthesia.

DOG DOSAGE

Induction of general anesthesia in dogs: Induction dose guidelines are based on data from the field study (see EFFECTIVENESS) and range between 1.5 – 4.5 mg/kg for dogs that did not receive a preanesthetic, and between 0.2 – 3.5 mg/kg for dogs that received a preanesthetic. The ALFAXAN induction dose in the field study was reduced by 23-50% depending on the combination of preanesthetics (dose sparing effect). Dose sparing of ALFAXAN will depend on the potency, dose, and time of administration of the various preanesthetics that are used prior to induction. To avoid anesthetic overdose, titrate the administration of ALFAXAN against the response of the patient. In the field study, the use of a preanesthetic appeared to decrease the occurrence of apnea following ALFAXAN induction in dogs.

In dogs, ALFAXAN usually produces recumbence within 60 seconds after the start of injection, and permits intubation within 1 – 2 minutes, irrespective of preanesthetic. The duration of anesthesia from a single induction dose is approximately 5 – 10 minutes in the unpreanesthetized dog. If a preanesthetic is used, anesthetic duration may be longer, depending on the class and dose of preanesthetic. Individual anesthesia times vary.

Examples from the field study of average induction doses (and ranges) for dogs that received various preanesthetics are presented as dosing guidelines in the table. The table is for guidance only. The actual induction dose should be based on patient response.

Table 3: ALFAXAN Induction Dose Guidelines: DOGS

Preanesthetic	Average ALFAXAN induction dose (and range) in mg/kg	Number of dogs
No preanesthetic	2.2 (1.5-4.5)	17
Benzodiazepine + opioid + acepromazine	1.7 (0.9-3.5)	39
Opioid + acepromazine	1.6 (0.6-3.5)	80
Alpha$_2$-agonist	1.1 (0.21-2.00)	9

Additional doses of ALFAXAN similar to those used for maintenance (1.2 – 2.2 mg/kg) may be administered to facilitate intubation.

Maintenance of general anesthesia in dogs: Following induction of anesthesia with ALFAXAN and intubation, anesthesia may be maintained using intermittent ALFAXAN intravenous boluses or an inhalant anesthetic agent. A maintenance bolus containing 1.2 – 1.4 mg/kg provides an additional 6 - 8 minutes anesthesia in preanesthetized dogs. A dose of 1.5 – 2.2 mg/kg provides an additional 6 - 8 minutes of anesthesia in unpreanesthetized dogs. Clinical response may vary, and is determined by the dose, rate of administration, and frequency of maintenance injections.

ALFAXAN maintenance dose sparing is greater in dogs that receive a preanesthetic. Examples from the field study of maintenance doses for preanesthetized and unpreanesthetized dogs are presented as guidelines in the table. Maintenance dose and frequency should be based on the response of the individual patient.

Table 4: ALFAXAN Maintenance Dose Guidelines: DOGS

	Preanesthetized dogs	Unpreanesthetized dogs
Maintenance anesthesia doses	1.2 – 1.4 mg/kg	1.5 – 2.2 mg/kg
Mean duration of anesthesia	6 – 8 minutes	6 – 8 minutes

In the field study, recovery times (extubation to head lift) following ALFAXAN maintenance anesthesia averaged 22 minutes in dogs that did not receive a preanesthetic, and 15 minutes in preanesthetized dogs.

Inhalant anesthetic maintenance of general anesthesia in dogs: Additional low doses of ALFAXAN, similar to a maintenance dose, may be required to facilitate the transition to inhalant maintenance anesthesia.

II. EFFECTIVENESS: CATS

A. Dosage Characterization:

The following 3 Australian field studies adequately characterized doses for ALFAXAN as an anesthetic in cats.

Study #1 Title: The effectiveness of alfaxalone-cyclodextrin in cats

Type of study: Field study

Investigators: Six veterinary clinics in Australia

Study Design: A total of 107 cats (48 male, 57 female, 2 unspecified) requiring anesthesia were enrolled in this study. Most cats (60%) were young and healthy, ranging in age from 1 year up to 14 years. Most (73%) of the procedures conducted under anesthesia were surgeries for ovariohysterectomy or castration.

Dose: Suggested IV dose rates were 2-4 mg/kg for induction, using the lower end of this range for preanesthetized cats. However, ALFAXAN was administered 'to effect'; the dose was determined by each patient's response.

Test Article: The test article was a lyophilized complex of ALFAXAN with cyclodextrin reconstituted to 10 mg/mL ALFAXAN with sterile buffer solution. The reconstituted solution differed from the final market formulation only in the buffer component.

Results: Acepromazine (with atropine in a few cases) was used in 63% of cases prior to the induction of anesthesia with ALFAXAN. Induction doses ranged from 2.1 – 10.0 mg/kg, with 90% of cases being induced within the range 2 – 8 mg/kg, and 60% within the range 2 – 5 mg/kg, as shown in the following table.

The following table describes the total ALFAXAN dose in mg/kg in preanesthetized or unpreanesthetized cats when used for induction only (Table 5a), induction + ALFAXAN maintenance bolus doses (Table 5b), and induction followed by maintenance inhalant anesthesia (Table 5c).

Table 5a: IV ALFAXAN induction dose (mg/kg); no maintenance anesthesia

Preanesthesia	NO	YES
Number of Cases	6	35
ALFAXAN Induction Dose Range (mean) in mg/kg	4.2 - 5.4 (4.7)	2.0 - 10.0 (5.2)

Table 5b: IV ALFAXAN induction dose with ALFAXAN maintenance anesthesia (mg/kg)

Preanesthesia	NO	YES
Number of Cases	18	8
ALFAXAN Induction Dose Range (mean) in mg/kg	2.5 - 7.1 (4.4)	3.3 - 6.7 (4.8)
ALFAXAN Total Dose* Range (mean) in mg/kg	4.5 - 10.9 (7.1)	5.0 - 9.2 (6.8)

*Total dose = induction + all maintenance bolus doses

Table 5c: IV ALFAXAN induction dose (mg/kg) followed by inhalant anesthesia

Preanesthesia	NO	YES
Number of Cases	1	15
ALFAXAN Induction Dose Range (mean) in mg/kg	2.9 (2.9)	2.1 -7.7 (4.3)

When ALFAXAN was used as the sole anesthetic agent, maintenance doses were used in 40% of the cats for procedures such as spaying, and some castrations. Total doses necessary for these procedures were 5.0 – 9.2 mg/kg when acepromazine was used for preanesthesia, and 4.5 – 10.9 mg/kg in the absence of acepromazine. Anesthesia was subjectively rated as "good" in 92% of cases, and "poor" to "moderate" in 5% of cases. Recovery was regarded as "good" to "very good" in 82% of cases.

Adverse reactions were reported in 10 (of 107) cats. Six cats were reported as "jumpy" during recovery. One cat, reported as being aggressive, experienced respiratory depression during induction and recovered after intubation. Other adverse reactions included retching, ineffectiveness (requiring additional doses during induction), and redness of the ear.

Conclusion: ALFAXAN was satisfactorily used at induction doses of 2-10 mg/kg IV in cats to produce anesthesia for procedures requiring light anesthesia and for intubation prior to maintenance with inhalant anesthesia. Anesthesia was satisfactorily maintained using ALFAXAN IV boluses or inhalant anesthesia.

Study #2 Title: The effect of induction and maintenance doses of IV ALFAXAN on the time to head-lift and sternal recumbency.

Investigators: Six veterinary clinics in Australia

Study Design: A total of 76 cats requiring anesthesia were enrolled in this study. Sixty-one cats were young and healthy, between 3-12 months of age. Fifty-five of the procedures conducted under anesthesia were surgeries for either ovariohysterectomy or castration.

Dose: Suggested IV dose rates were 3-5 mg/kg for induction, using the lower end of this range for preanesthetized cats; however, ALFAXAN was administered 'to effect'. The dose was determined by each patient's response.

Test Article: The test article was a lyophilized complex of alfaxalone with cyclodextrin reconstituted to 10 mg/mL alfaxalone with sterile buffer solution. The reconstituted solution differed from the final market formulation only in the buffer component.

Results: In 67 cases, acepromazine was used prior to induction, with atropine administered in approximately half of the cases receiving acepromazine. The induction dose of ALFAXAN ranged from 2.4 - 10.0 mg/kg. Fifty-five cases were induced using 3 - 6 mg/kg, 45 of which received 3 - 5 mg/kg. Thirty procedures lasted between 3 - 20 minutes and required no maintenance doses. Twenty-one cases received ALFAXAN for induction followed by maintenance with inhalant anesthesia. ALFAXAN was used as the sole induction and maintenance anesthesia agent in the remaining 25 cases. The dose, procedure, and recovery times are summarized in the following table.

Table 6: Induction and maintenance doses

	IV ALFAXAN with no maintenance anesthesia	IV ALFAXAN with maintenance anesthesia using ALFAXAN boluses	IV ALFAXAN followed by inhalant anesthesia
Number of Cases	30	25	21
ALFAXAN Induction Dose Range (Mean) in mg/kg	3.0 – 10.0 (6.1)	2.4 – 9.2 (5.2)	3.1 – 7.0 (4.5)
ALFAXAN Total Dose* Range (Mean) in mg/kg	3.0 – 10.0 (6.1)	3.6 – 13.3 (7.5)	3.1 – 7.0 (4.5)
Procedure Time Range (Mean) in minutes	3 – 20 (7.6)	3 – 17 (11.5)	6 – 65 (26.5)
Time to Sternal Recumbency Range (Mean) in minutes	23 – 120 (50.2)	12 – 100 (56.8)	11 – 107 (63.5)

*Total dose = induction + all maintenance doses

Induction doses of ALFAXAN ranged between 2.4-10 mg/kg. Incremental maintenance doses up to a total of 3 – 7 mg/kg for short surgical procedures such as castration, and up to 8 – 13 mg/kg for longer surgical procedures were required. Maintenance doses up to a total of 13.3 mg/kg were also administered for a range of procedures. Adverse reactions were recorded in 3 cats. One cat was excitable during recovery, 1 cat was retching during recovery, and 1 cat was too lightly anesthetized (ineffectiveness) during the procedure.

Conclusion: ALFAXAN was satisfactorily administered 'to effect' at induction doses of 2.4-10 mg/kg IV in cats to produce anesthesia for procedures requiring light anesthesia and for intubation prior to maintenance with inhalant anesthesia.

Study #3 Title: The effectiveness of ALFAXAN anesthetic injection in cats.

Type of study: Field study

Investigators: Five veterinary clinics in Australia

Study Design: Ninety (90) cats (53 male, 36 female, 1 not specified) of 11 breeds were enrolled in this study conducted at 5 veterinary hospitals in Australia for various procedures. The cats ranged in age from 2 months to 17 years of age, and in bodyweight from 0.5 kg to 9.6 kg (mean 3.5 kg). A total of 17 sole or combined procedures were performed, most of which involved castration (40%), spaying (17%) and dental procedures (12%). While most of the cats were healthy, a proportion (22%) of the total had pre-existing medical conditions which required treatment under anesthesia.

Dose: Although potentially suitable dose ranges were suggested to participating veterinarians (3-5 mg/kg), ALFAXAN was administered 'to effect'. The dose was determined by each patient's response.

Test Article: The test article was a lyophilized complex of alfaxalone with cyclodextrin reconstituted to 10 mg/mL alfaxalone with sterile buffer solution. The reconstituted solution differed from the final market formulation only in the buffer component.

Results: In 93% of cases, preanesthesia was used prior to the induction of anesthesia with ALFAXAN. The preanesthetic used was acepromazine alone (59% of cases) or in combination with atropine, butorphanol tartrate, or xylazine. Some cases received carprofen. The dose, procedure and recovery times are summarized in the following table.

Table 7: Induction and maintenance doses

	IV ALFAXAN with no maintenance anesthesia	IV ALFAXAN with maintenance anesthesia using ALFAXAN boluses	IV ALFAXAN followed by inhalant anesthesia
Number of Cases	39	27	7
ALFAXAN Induction Dose Range	1.0 - 10.0 (4.7)	1.3 - 10.0 (4.2)	2.5 - 3.8 (3.2)
ALFAXAN Total Dose*	1.0 - 10.0 (4.7)	1.4 - 20.0 (6.8)	3.3 - 6.9 (4.7)
Procedure Time Range (mean)	1 - 21 (8.9)	1 - 47 (17)	15 - 90 (36.8)
Time Range to Sternal	10 - 90 (36)	20 - 120 (56)	60 - 90 (76)

*Total dose = induction + all maintenance doses

The induction doses of ALFAXAN used in this study ranged from 1 to 10.0 mg/kg, with a mean of 4.4 mg/kg for induction of anesthesia and short surgical procedures. Without maintenance doses, procedures ranging in length from 1 minute to 21 minutes were possible. Maintenance doses were necessary when longer procedures (up to 47 minutes) were undertaken using ALFAXAN as the sole anesthetic agent (up to a total dose of 20 mg/kg). The quality of induction, anesthesia and recovery was generally reported as good, and no life-threatening adverse events were reported.

Conclusion: A single dose of ALFAXAN in the range 1 – 10 mg/kg IV induced anesthesia for short procedures and for intubation prior to inhalant anesthesia. The anesthetic agent proved satisfactory for a range of procedures.

B. Substantial Evidence of Effectiveness

Cat Field Study

a. Title (Study No.): A multicenter field study in cats evaluating the effectiveness and safety of ALFAXAN administered to veterinary patients for induction and maintenance of anesthesia (JX9604.07-C006).

b. Type of Study: Field study

c. Study Dates: April 27-December 19, 2004

d. Investigators and Locations:

Table 8: Investigators and locations

Dr. Janet Cridland Petersham, NSW, Australia	Dr. Marcus Gunew Mt Gravatt, QLD, Australia
Dr. Gwilym Hunt Leichhardt, NSW, Australia	Dr. Fran Musca Paddington, QLD, Australia
Dr. Andrew Herron Randwick, NSW, Australia	Dr. Warren Foreman Trinity Gardens, SA, Australia
Dr. Julie Handley Chatswood Hills, QLD, Australia	Dr. Phil Hutt Morphett Vale, SA, Australia
Dr. Tony Thelander Chermside, QLD, Australia	Dr. Julia Nicholls Prospect, SA, Australia

e. Study Design:

1) Purpose: This field study assessed the clinical effectiveness and safety of 10 mg/mL injectable ALFAXAN (alfaxalone) in cats for the induction and maintenance of anesthesia and for induction of anesthesia followed by maintenance with an inhalant anesthetic. ALFAXAN was used as the sole anesthetic agent or was administered in conjunction with commonly used preanesthetics.

2) Description of Test Animals: Two hundred and seven (207) cats including males and females of 19 breeds or mixed breeds, between the ages of 1 month and 17.5 years, weighing between 0.6 and 9 kilograms, were successfully anesthetized using ALFAXAN for various types of surgery and procedures requiring anesthesia.

3) Treatment Groups: The cats were enrolled and assigned to one of four treatment groups based on their anesthetic requirement.

Table 9: Treatment groups

Group	Preanesthetic	Induction	Maintenance	Cases (of 207 total)
1	None	ALFAXAN	ALFAXAN	33
2	Yes	ALFAXAN	ALFAXAN	70
3	Yes	ALFAXAN	Halothane	18
4	Yes	ALFAXAN	Isoflurane	86

4) Dosage Form: ALFAXAN (alfaxalone) 10 mg/mL for intravenous (IV) injection in the final market formulation.

5) Administration: ALFAXAN was administered IV over approximately 60 seconds. ALFAXAN was administered once, to effect (until intubation), up to a maximum dose of 5.0 mg/kg. Additional doses were administered if clinically necessary to achieve intubation. When used for maintaining anesthesia, ALFAXAN was administered to effect in increments of approximately 1 to 2 mg/kg bodyweight as needed. Preanesthetics and inhalant maintenance anesthetics were administered at label recommended routes and rates.

6) Preanesthetics: Preanesthetic was administered 20-30 minutes prior to anesthetic induction by either subcutaneous (SC) or intramuscular (IM) injection. Preanesthetic drugs were administered only once to each cat.

Table 10: Preanesthetic, dose, and route of administration

AGENT	DOSE	ROUTE
Acepromazine	0.03 mg/kg	SC
Medetomidine	0.005 mg/kg	IM
Xylazine	0.3 mg/kg	SC/IM
Midazolam	0.2 mg/kg	IM
Butorphanol	0.4 mg/kg butorphanol	SC/IM
Morphine/Acepromazine	0.3 mg/kg morphine/0.03 mg/kg acepromazine	SC/IM
Buprenorphine	0.03 mg/kg	SC/IM

7) Study variables:

Anesthesia Variables:

Time to Onset of Anesthesia (seconds): The time (to the nearest second using digital stopwatch) at which the intubation was successful was recorded as the onset of anesthesia.

Total Dose for Induction (mL): The difference in volume between ALFAXAN loaded into the syringe, and the volume remaining following intubation. Bolus doses of ALFAXAN when used for maintenance were recorded as amount administered in mL.

Duration of Immediate Post-induction Apnea (IPIA): Time in minutes/seconds of the first inspiratory effort after intubation. Apnea was recorded if the time was ≥30 seconds. If apnea occurred the cat received one breath every 30 seconds unless the SpO_2 was ≥87%.

Induction Score (quality): The quality of induction was scored as acceptable (3 = smooth, cat readily intubated), intermediate (2 = required additional induction agent, difficult to intubate, large amount of jaw tone), or unacceptable (1 = intubation not possible even with additional induction agent).

Anesthetic Quality: The quality of anesthesia between intubation and extubation was scored as excellent (3 = maintains recumbency and immobilization, minimal muscle tremors, no response to noise), acceptable (2 = some movement, short duration of recumbency, attempts to rise, muscle tremors), or unacceptable (1 = did not become recumbent, muscle rigidity with twitching, vocalization, defecation, responds to noise).

Recovery Time: Time between extubation and the first purposeful movement.

Recovery Score (quality): The quality of recovery was scored as excellent (4 = completely smooth recovery), good (3 = smooth recovery with minor paddling or tremors), fair (2 = paddling, thrashing), or poor (1 = rough recovery, vocalization, opisthotonos, seizures).

Physiological Variables:
Indirect Systolic Blood Pressure (mmHg): Doppler Ultrasound measured prior to preanesthesia (if possible), 10 minutes after preanesthesia, 20-30 minutes before induction, and at intervals of 5-10 minutes after induction with ALFAXAN until extubation.

Heart Rate (beats per minute): Measured before and after preanesthesia (peripheral artery), before induction, and after induction at intervals of 5-10 minutes until no longer recumbent.

Respiratory Rate (RR, breaths per minute): Measured before and after preanesthesia, prior to induction, and every 5-10 minutes until the first purposeful movement. RR was assessed visually using chest wall or rebreathing bag movement.

Rectal Temperature: Measured (electronic thermometer) at preanesthesia physical examination and at the conclusion of anesthesia during recovery.

Oxygen Saturation of Hemoglobin (SpO_2%): Oxygen saturation of hemoglobin percentage (SpO_2) measured by pulse oximetry, was monitored after induction and at 5-10 minute intervals until movement prevented use of the pulse oximeter.

Mucosa color: Assessed before and after preanesthesia, prior to induction, and at intervals of 5-10 minutes until the first purposeful movement. Gingival or conjunctival mucosa was visually inspected and scored as recorded as pink/moist (normal), pale, red/injected, blue, yellow, or other.

8) Statistical Methods: Descriptive statistics for the study variables were reported by treatment group and by preanesthetic categories within treatment group. Physiological variables, anesthetic times, induction dose, maintenance doses, and anesthesia scores were summarized by treatment groups as mean, standard deviation, minimum and maximum.

f. Results:

The results from the 4 treatment groups were further evaluated according to preanesthetic. Of the 207 cats in the study, 174 cats received one or more preanesthetics and 33 received no preanesthetic. No incompatibilities were noted when ALFAXAN was used in the presence of preanesthetics.

Table 11: Case grouping for cats with or without preanesthetic or preanesthetic combinations:

Preanesthetic class	Preanesthetics	No.
Benzodiazepine + phenothiazine	Midazolam with either acepromazine or atropine or both	23
Alpha$_2$-adrenergic agonist + phenothiazine	Medetomidine or xylazine with either acepromazine or atropine or both	8
Opioid + phenothiazine	Butorphanol or buprenorphine or morphine with either acepromazine or atropine or both	96
Alpha$_2$-adrenergic agonist	Medetomidine or xylazine with or without atropine (no acepromazine)	7
Opioid	Butorphanol or buprenorphine or morphine with or without atropine (no acepromazine)	2
Benzodiazepine + alpha$_2$-adrenergic agonist + phenothiazine	Midazolam and medetomidine or xylazine with either acepromazine or atropine or both	3
Alpha$_2$-adrenergic agonist + opioid + phenothiazine	Medetomidine or xylazine and butorphanol or buprenorphine or morphine with either acepromazine or atropine or both	8
Benzodiazepine + opioid + phenothiazine	Midazolam and butorphanol or buprenorphine or morphine with either acepromazine or atropine or both	26
No premedications	None	34
	TOTAL	207

1) Procedures: The duration of anesthesia ranged between 6.6 and 122.9 minutes.

Table 12: Procedure and Number of Cats

Procedure	Number of cats*
Dental prophylaxis	73
Castration	50
Ovariohysterectomy (OHE)	44
Microchip insertion	10
Grooming	9
Abscess	6
Biopsy – gum/oral	4
Radiographs	4
Dental prophylaxis with extractions	3
Tattoo	3
Tooth extraction	3
Wound + suture	3
Blood donation	2
Cryosurgery on nose	2
Lump removal	2
Ultrasound - abdominal	2
Amputation - tail	1
Biopsy	1
Cystocentesis	1
Ear pinna ablation	1
Flush tear ducts	1
Infected area removed from skin	1
Insert drain	1
Left eye enucleation	1
Mass removal from pharynx	1
Nasopharyngeal endoscopy	1
OHE late term pregnancy	1
Rectal exam and scraping	1
Removal cancerous skin	1
Remove dermal cyst from conjunctiva	1
Remove mammary tumor	1
Wound debridement (degloving injury)	1

* Each cat may have undergone more than one procedure.

Anesthesia Variables:

2) *Time to Onset of Anesthesia (seconds):* The onset of anesthesia (intubation) occurred within 1-2 minutes after the start of ALFAXAN injection in all cats. Cats without preanesthesia took slightly longer (98 seconds) compared to preanesthetized cats (84 seconds). The duration of induction was not affected by any specific preanesthetic or by the administration of atropine.

3) *Induction and Maintenance Doses:*

Induction doses: Induction doses averaged 3.3 mg/kg body weight for all cats. Doses ranged between 1.0 – 10.8 mg/kg for cats that received a preanesthetic, and between 2.2 - 9.7 mg/kg for cats that did not receive a preanesthetic during the study.

Table 13: Induction does comparison by preanesthetics class*

Preanesthetic	Average ALFAXAN induction dose (and range) in mg/kg	Number of cats
No preanesthetic	4.0 (2.2-9.7)	33
Opioid + phenothiazine	3.2 (1.1-10.8)	96
Benzodiazepine + opioid +phenothiazine	2.3 (1.2-5.0)	26
Alpha$_2$-adrenergic agonist with/without phenothiazine	3.6 (1.1-5.0)	15
Alpha$_2$-adrenergic agonist + phenothiazines with/without benzodiazepine or opioid	2.9 (1.0-3.9)	11
Benzodiazepine + phenothiazine	3.6 (1.5-7.1)	23
Opioid	6.0 (2.0-10)	2

*see Table 11 above for specific preanesthetics in these classes and Table 10 for their doses.

The ALFAXAN induction dose in the field study was reduced by 10 - 43%, depending on the preanesthetic (dose sparing effect). Dose sparing of ALFAXAN depends on the potency, dose, and time of administration of the various preanesthetics that are used prior to induction.

ALFAXAN Maintenance: Maintenance doses were recorded for 76 cats, including 24 unpreanesthetized cats, and 52 cats that received preanesthetics.

Table 14: Number of maintenance boluses

# boluses	Unpre-anesthetized	Pre-anesthetized	Total
1	7	16	23
2	7	10	17
3	4	12	16
4	4	7	11
5	2	3	5
6	0	1	1
7	0	1	1
8	0	0	0
9	0	2	2
Total	24	52	76

Seventy-two (of 76) cats were maintained using between 1 - 5 ALFAXAN boluses. Average maintenance doses ranged between 0.9 - 1.3 mg/kg in preanesthetized cats and 0.9 – 1.6 mg/kg in unpreanesthetized cats. Doses were given to effect and titrated

against the response of the individual patient. Maintenance doses (mg/kg) and number of boluses administered are summarized as follows:

Table 15a: ALFAXAN maintenance boluses and mean total dose of each of these boluses (mg/kg) in unpreanesthetized cats

# boluses	# cats	mean	SD	min	max
1	24	1.6	0.77	0.2	3.4
2	17	1.4	0.65	0.6	2.6
3	10	1.5	0.38	1.1	2.2
4	6	1.4	0.45	1	2.1
5	2	0.9	0.35	0.6	1.1

Table 15b: ALFAXAN maintenance boluses and mean total dose of each of these boluses (mg/kg) in preanesthetized cats

# boluses	# cats	mean	SD	min	max
1	52	1.3	0.67	0.5	4.8
2	36	1.3	0.8	0.4	4.8
3	26	1.2	0.45	0.6	2.5
4	14	1.1	0.46	0.6	2.2
5	7	0.9	0.54	0.6	2.1

Depending on dose, rate of administration, and frequency of maintenance bolus injections, a maintenance bolus containing 1.1 – 1.3 mg/kg provides an additional 7 - 8 minutes of anesthesia in preanesthetized cats. A dose of 1.4 - 1.5 mg/kg provides an additional 3 - 5 minutes anesthesia in unpreanesthetized cats.
The intervals between maintenance boluses are summarized below.

Table 16a: Interval between maintenance boluses (minutes) in unpreanesthetized cats

# boluses	# cats	mean	SD	min	max
bolus 1	24	-	-	-	-
bolus 2	17	4.9	3.45	0.83	15.13
bolus 3	10	2.8	3.05	0.67	11.10
bolus 4	6	5.2	4.25	1.70	12.32
bolus 5	2	8.2	8.71	2.07	14.38

Table 16b: Interval between maintenance boluses (minutes) in preanesthetized cats

# boluses	# cats	mean	SD	min	max
bolus 1	52	-	-	-	-
bolus 2	36	7.6	3.85	0.63	19.97
bolus 3	26	7.4	3.00	0.67	13.90
bolus 4	14	7.1	3.97	2.33	17.70
bolus 5	7	7.9	2.64	4.37	12.40

*Interval (minutes) represents the time between administration of preceding bolus and current bolus.

Inhalant Maintenance: Following ALFAXAN induction, 18 (of 104) cats were maintained using halothane and 86 (of 104) were maintained using isoflurane. Inhalant concentration (%) was recorded at 5-10 minute intervals. Average

concentrations were similar among the various preanesthetic groups and no incompatibilities were noted relating to the use of either inhalant when ALFAXAN was used for induction.

4) *Apnea:*

Immediate Post-induction Apnea: All cats were intubated and received supplemental oxygen. Post-induction apnea (≥30 seconds) was recorded in 32 cats treated with ALFAXAN. Apnea lasted ≥60 seconds in 12 of these 32 cats. Apnea lasting ≥30 seconds occurred in 28 (of 169) preanesthetized cats (16.6%) and 4 (of 33) unpreanesthetized cats (12.1%) after induction with ALFAXAN. Apnea lasting ≥60 seconds occurred in 9 of the 28 apneic preanesthetized cats (5.3%) and 3 of the 4 apneic unpreanesthetized cats (9.1%) after induction with ALFAXAN. No particular preanesthetic was more or less likely to result in apnea after ALFAXAN induction.

Maintenance Apnea: There was no apnea observed during maintenance anesthesia during this study.

5) *Induction Quality:* Induction scores were acceptable (scored highest) in >90% of the cats.

Table 17: Induction scores and number of cats

Score	# Unpreanesthetized cats	# Preanesthetized cats
1 (unacceptable)	0	1
2 (intermediate)	3	7
3 (acceptable)	30	166
Totals	33	174

6) *Anesthesia Quality:* Quality of anesthesia scores were satisfactory as follows:

Table 18: Anesthesia scores and number of cats

Score	# Unpreanesthetized cats	# Preanesthetized cats
1 (unacceptable)	1	0
2 (acceptable)	3	11
3 (excellent)	29	162
Missing score	0	1
Totals	33	174

7) *Recovery Times:* Recovery times were evaluated during the study as the time between endotracheal extubation and head lift, and time between extubation and first purposeful movement.

Time to Head Lift: The mean time to head lift ranged between 5.4 and 17.0 minutes.

Table 19: Extubation to head lift (minutes) by treatment group*

	Group 1	Group 2	Group 3	Group 4
Number	33	69	18	86
Mean	14.70	16.96	5.39	12.8
SD	12.29	14.21	4.12	16.38
Max	48.58	59.48	12.97	94.03
Min	0.37	0	0	0
Missing	0	1	0	0

*Group 1 did not receive a preanesthetic; groups 1 and 2 received ALFAXAN maintenance anesthesia; group 3 cats were maintained using halothane; group 4 cats were maintained using isoflurane.

Time to First Purposeful Movement: The mean time to purposeful movement ranged between 13.4 and 32.3 minutes across treatment groups.

Table 20: Extubation to first purposeful movement (minutes)

	Group 1	Group 2	Group 3	Group 4
Number	33	69	18	86
Mean	25.52	32.30	13.4	21.7
SD	18.51	24.77	11.88	21.67
Max	87.27	129.93	51.1	95.35
Min	1.02	0.55	1.48	1.85
Missing	0	1	0	0

* Group 1 did not receive a preanesthetic; groups 1 and 2 received ALFAXAN maintenance anesthesia; group 3 cats were maintained using halothane; group 4 cats were maintained using isoflurane.

8) Recovery Score (quality of recovery): Unpreanesthetized cats had the highest percentage of poor or fair recovery scores.

Table 21: Recovery Score: Number of cats assessed at each score level

	Group 1*	Group 2	Group 3	Group 4
1 (Poor)	0	0	0	0
2 (Fair)	10	5	2	5
3 (Good)	10	24	5	20
4 (Excellent)	13	41	11	61
Total	33	70	18	86
% scores = 1 or 2	30.3	7.1	11.1	5.8
% scores = 3 or 4	69.7	92.9	88.9	94.2

*unpreanesthetized

Physiological Data (see Adverse Reactions table below):

9) *Indirect Systolic Blood Pressure (mmHg)*: Systolic blood pressure (SBP) was evaluated using Doppler and pneumatic cuff technology over the radial artery. SBP before anesthetic induction was similar amongst treatment groups. ALFAXAN maintained cats showed a maximal decrease in SBP of approximately 20-30 mmHg; cats maintained with an inhalant maintenance anesthetic showed a decrease of

approximately 50 mmHg. Average SBP increased toward baseline during recovery. Hypertension (defined as >165 mmHg) occurred at least once in 23 cats and hypotension (defined as ≤ 90 mmHg) in 92 cats.

10) Pulse Rate (beats per minute): Mean Pulse Rate (PR) decreased by approximately 5% after induction using ALFAXAN. Bradycardia (≤ 90 beats/minute) occurred in 10 cats and tachycardia (≥ 180 beats per minute) occurred in 61 cats. Cardiac function remained stable and clinically acceptable across cats in all treatment groups.

11) Respiratory Rate (breaths per minute): Mean respiratory rates (RR) in all groups decreased immediately after induction to approximately 50% of their resting rate, returning toward baseline during recovery. Bradypnea (≤ 10 breaths/minute) occurred in 16 cats during the study.

12) Rectal Temperature: The average rectal body temperature before anesthesia ranged between 38-39°C; during recovery, temperatures ranged between 37-37.5°C. External heat sources were used to prevent extreme decreases in core body temperature during anesthesia and recovery. Hypothermia (defined as <97 °F or <36 °C) occurred in 10 cats. No hyperthermic temperatures were recorded.

13) Oxygen Saturation of Hemoglobin (SpO_2%): Hypoxia (SpO_2 <85%) occurred in 4 cats during the study.

14) Mucosa color: Mucosal color remained stable across cats in all treatment groups.

g. Adverse Reactions: The following table illustrates the number of cats displaying each adverse reaction during the field study. Many reflect the physiological effects associated with general anesthesia.

Table 22: Adverse Reactions in Cat Field Study

Adverse Reaction	Number of Cats[a] (total of 207)
Hypotension (≤90 mm Hg)	92
Tachycardia (≥180 bpm)	61
Apnea (≥30 seconds)	32 (of 202)
Hypertension (>165 mm Hg)	23
Bradypnea (RR <10 breaths/min)	16
Apnea (≥60 seconds)	12 (of 202)
Bradycardia (≤90 beats/min)	10
Hypothermia (<97 °F)	10
Hypoxia (SpO_2 <85%)	4
Emesis	1
Unacceptable Anesthesia Quality	1

[a] Each cat may have experienced more than one adverse reaction

Additional adverse reactions for cats included vocalization, paddling, and muscle tremors.

h. Conclusions: This study confirmed the clinical effectiveness and safety of ALFAXAN when administered to cats as the sole anesthetic agent for the induction and maintenance of anesthesia, when used in conjunction with commonly used preanesthetic agents, and when administered for induction of anesthesia with subsequent maintenance by inhalant anesthetics.

III. EFFECTIVENESS: DOGS

A. Dosage Characterization:

Title: The cardiovascular and respiratory safety of ALFAXAN when administered to dogs intravenously which have been premedicated with acepromazine, medetomidine, midazolam or butorphanol.

Type of study: Laboratory study

Study Director: Dr. William W. Muir, DVM, PhD, DACVA, DACVECC
Columbus, OH

The purpose of this study was to determine the effective dose of ALFAXAN when administered IV to unpreanesthetized dogs and dogs preanesthetized with acepromazine, medetomidine, midazolam or butorphanol, and to evaluate the compatibility of ALFAXAN in the presence of various preanesthetics.

Forty-eight (48) healthy Beagle dogs (24 male, 24 female) weighing 8.0-15.8 kg and 0.8-2.0 years of age were randomly assigned to 8 groups, each containing 6 animals (3 males and 3 females). The dogs were given various preanesthetics. One group received saline in place of the preanesthetic. Twenty-five minutes after administration of the preanesthetics, ALFAXAN (alfaxalone 10 mg/mL) Anesthetic Injection (the final market formulation) was administered by intravenous injection (over 60 seconds), until the dog was anesthetized (given 'to effect').

Variables measured included duration of non-responsiveness to noxious stimulus including mechanical (toe pinch) and electrical (buccal mucosal) stimulation, duration of anesthesia, overall anesthesia score, and total dose of ALFAXAN administered.

The average induction dose of ALFAXAN, the overall anesthetic score, and the average duration of anesthesia (intubation to extubation) are presented in the following table:

Table 23: Mean induction dose, anesthetic score, and duration of anesthesia by treatment group

Preanesthetic (IM)	ALFAXAN Induction Dose (mg/kg)	Mean Overall Anesthetic Score (1 = best/3 = worst)	Mean Duration of Anesthesia (min)
Medetomidine 40 mcg/kg	1.0	1.0	52.4
Acepromazine 1.1 mg/kg	1.2	1.0	9.1
Acepromazine 0.2 mg/kg	1.4	1.0	10.2
Acepromazine 0.05 mg/kg	1.4	1.3	6.9
Butorphanol 0.2 mg/kg	1.4	1.3	7.9
Medetomidine 4 mcg/kg	1.6	1.3	10.3
None (0.9% saline)	1.7	1.3	6.0
Midazolam 0.2 mg/kg	1.8	2.0	8.0

Conclusion: Doses given to effect were between 1 – 2 mg/kg IV and resulted in satisfactory anesthesia. Preanesthetics were compatible with ALFAXAN and provided varying amounts of ALFAXAN dose sparing. This study supports the dose of 1 - 2 mg/kg ALFAXAN administered IV.

B. Substantial Evidence of Effectiveness:

Dog Field Study

a. Title (Study No.): A multicenter clinical trial in dogs evaluating the effectiveness and safety of ALFAXAN administered to veterinary patients for induction and maintenance of anesthesia (JX9604.03-C009)

b. Type of Study: Field Study

c. Study Dates: October 2003 to August 2004

d. Investigators and locations:

Table 24: Investigators and locations:

Dr. Gwilym Hunt Leichhardt, NSW, Australia	Dr. Rod Starr Medowie, NSW, Australia
Dr. Mark Hocking Gladesville, NSW, Australia	Dr. Andrew Herron Randwick, NSW, Australia
Drs. Heidi Beruter and Amanda Cole Pendle Hill, NSW, Australia	Dr. Mark Simpson West Wallsend, NSW, Australia
Dr. Catherine Coyle Kirrawee, NSW, Australia	Dr. Michael Hayward Gungahlin, ACT, Australia
Dr. Janet Cridland Petersham, NSW, Australia	

e. Study Design:

1) Purpose: This field study assessed the clinical effectiveness and safety of 10 mg/mL injectable ALFAXAN (alfaxalone) in dogs for the induction and maintenance of anesthesia and for induction of anesthesia followed by maintenance with an inhalant anesthetic. ALFAXAN was used as the sole anesthetic agent or was administered in conjunction with commonly used preanesthetics.

2) Description of Test Animals: One hundred eighty-two dogs (101 male and 81 females of 54 breeds), between the ages of 3 months and 13 years, weighing between 2.4 and 41.4 kg, were successfully anesthetized using ALFAXAN for various types of surgery or procedures requiring anesthesia.

3) Treatment Groups: The dogs were enrolled and assigned to 1 of 4 treatment groups based on their anesthetic requirement.

Table 25: Treatment groups

Group	Preanesthetic	Induction	Maintenance	# Cases (of 182 total)
1	None	ALFAXAN	ALFAXAN	17
2	Yes	ALFAXAN	ALFAXAN	47
3	Yes	ALFAXAN	halothane	28
4	Yes	ALFAXAN	isoflurane	90

4) Dosage form: ALFAXAN (alfaxalone) 10 mg/mL for intravenous (IV) injection in the final market formulation was used as the test drug.

5) Drug administration: ALFAXAN was administered IV over approximately 60 seconds. ALFAXAN was administered once, to effect (until intubation), up to a dose of 2.0 mg/kg. Additional doses were administered if clinically necessary to achieve intubation. When used for maintaining anesthesia, ALFAXAN was administered to effect in increments of approximately 0.5 - 0.7 mg/kg bodyweight as needed. Preanesthetics and inhalant maintenance anesthetics were administered at label recommended routes and rates.

6) Preanesthetics: Preanesthetic was administered 20 - 30 minutes prior to anesthetic induction either by subcutaneous (SC) or intramuscular (IM) injection. Preanesthetic drugs were administered only once to each dog.

Table 26: Preanesthetics, dose, and route of administration

Agent	Dose Rate	Route
Acepromazine maleate	0.03 mg/kg	SC
Atropine sulfate	0.04 mg/kg	SC
Medetomidine HCl	5-30 mcg/kg	IM
Midazolam HCl	0.2 mg/kg	IM
Butorphanol tartrate	0.3 mg/kg	SC
Morphine sulfate	0.3 mg/kg	SC
Carprofen	2.2 mg/kg	SC

7) Study variables:

Anesthesia Parameters:

Time to Onset of Anesthesia (seconds): The time (to the nearest second using digital stopwatch) at which the intubation was successful was recorded as the onset of anesthesia.

Total Dose for Induction (mL): The difference in volume between ALFAXAN loaded into the syringe, and the volume remaining intubation. Bolus doses of ALFAXAN when used for maintenance were recorded as amount administered in mL.

Duration of Immediate Post-induction Apnea (IPIA): Time in minutes/seconds of the first inspiratory effort after intubation. Apnea was recorded if the time was ≥30 seconds. If apnea occurred the cat received one breath every 30 seconds unless the SpO_2 was ≥87%.

Induction Score (quality): The quality of induction was scored as acceptable (3 = smooth, cat readily intubated), intermediate (2 = required additional induction agent, difficult to intubate, large amount of jaw tone), or unacceptable (1 = intubation not possible even with additional induction agent).

Anesthetic Quality: The quality of anesthesia between intubation and extubation was scored as excellent (3 = maintains recumbency and immobilization, minimal muscle tremors, no response to noise), acceptable (2 = some movement, short duration of recumbency, attempts to rise, muscle tremors), or unacceptable (1 = did not become recumbent, muscle rigidity with twitching, vocalization, defecation, responds to noise).

Recovery Time: Time between extubation and the first purposeful movement.

Recovery Score (quality): The quality of recovery was scored as excellent (4 = completely smooth recovery), good (3 = smooth recovery with minor paddling or tremors), fair (2 = paddling, thrashing), or poor (1 = rough recovery, vocalization, opisthotonos, seizures).

Physiological Variables:

Indirect Systolic Blood Pressure (mm Hg): Doppler Ultrasound measured prior to preanesthesia (if possible), 10 minutes after preanesthesia, 20-30 minutes before induction, and at intervals of 5-10 minutes after induction with ALFAXAN until extubation.

Heart Rate (beats per minute): Measured before and after preanesthesia (peripheral artery), before induction, and after induction at intervals of 5-10 minutes until no longer recumbent.

Respiratory Rate (RR, breaths per minute): Measured before and after preanesthesia, prior to induction, and every 5-10 minutes until the first purposeful movement. RR was assessed visually using chest wall or rebreathing bag movement.

Rectal Temperature: Measured (electronic thermometer) at preanesthesia physical examination and at the conclusion of anesthesia during recovery.

Oxygen Saturation of Hemoglobin (SpO_2%): Oxygen saturation of hemoglobin percentage (SpO_2) measured by pulse oximetry, was monitored after induction and at 5-10 minute intervals until movement prevented use of the pulse oximeter.

Mucosa color: Assessed before and after preanesthesia, prior to induction, and at intervals of 5-10 minutes until the first purposeful movement. Gingival or conjunctival mucosa was visually inspected and scored as recorded as pink/moist (normal), pale, red/injected, blue, yellow, or other.

8) Statistical Methods: Descriptive statistics for the study variables were reported by treatment group and by preanesthetic categories within treatment group. Physiological variables, anesthetic times, induction dose, maintenance doses, and anesthesia scores were summarized by treatment groups as mean, standard deviation, minimum, and maximum.

f. Results:

The results from the 4 treatment groups were further evaluated according to preanesthetic. Of the 182 dogs in the study, 159 treated dogs received one or more preanesthetics and 23 dogs received no preanesthetic. No incompatibilities were noted when ALFAXAN was used in the presence of preanesthetics.

Table 27: Number of dogs with or without preanesthetics:

Drug class combinations	Preanesthetics	No.
Opioid + phenothiazine	Butorphanol or Morphine with either Acepromazine or Atropine or both	80
Benzodiazepine +opioid + phenothiazine	Midazolam + Butorphanol or Morphine with either Acepromazine or Atropine or both	39
No preanesthetic	None	23
Phenothiazine	Acepromazine	17
$Alpha_2$-adrenergic agonist	Medetomidine +/- Atropine (no Acepromazine)	9
$Alpha_2$-adrenergic agonist + opioid + phenothiazine	Medetomidine + Butorphanol or Morphine with either Acepromazine or Atropine or both	6
Benzodiazepine + phenothiazine	Midazolam with either Acepromazine or Atropine or both	4
Opioid	Butorphanol or Morphine +/- Atropine (no Acepromazine)	3
$Alpha_2$-adrenergic agonist + phenothiazine	Medetomidine with either Acepromazine or Atropine or both	1
	TOTAL	182

1) *Procedures:* The duration of anesthesia ranged between 12.2 and 129.9 minutes.

Table 28: Procedure and Number of Dogs

Surgery/Procedure	Totals*
Castration	76
Ovariohysterectomy	61
Dentistry	46
Remove Dermal Tumors	15
Radiographs	14
Dew Claw Removal	4
Deciduous Canine Teeth Removal	3
Suture Wound	3
Anal Gland Abscess/Flush	2
Castration - Cryptorchid	2
Eye Examination	2
Hernia Repair (not specified)	2
Microchip	2
Pharyngeal Examination	2
Tail Amputation	2
Tooth Root Abscess	2
Corneal Ulcer Debridement	1
Cruciate Repair	1
Ear Cleaning	1
Ear Pluck	1
Entropion	1
Examination of Nasal Cavity	1
Exploratory Laparotomy	1
Hernia Repair - Inguinal	1
Hernia Repair - Umbilical	1
Meiobian Gland Removal	1
Nasal Scrape	1
Pyometra	1
Remove Oral Mass	1
Soft Palate Resection	1
Vaginal Polyp Examination	1
Wound Debridement	1

* Each dog may have undergone more than one procedure.

Anesthesia Parameters:

2) Time to Onset of Anesthesia (seconds):

The onset of anesthesia (intubation) occurred within 1-2 minutes after the start of the ALFAXAN injection in all dogs. Dogs without preanesthesia took slightly longer (87 seconds) compared to preanesthetized dogs (72 seconds). Induction time was not affected by any specific preanesthetic or by the administration of atropine.

3) Induction and Maintenance Doses:

Induction doses: The average induction dose for ALFAXAN was 2.2 mg/kg in unpreanesthetized dogs (range 1.5-4.5 mg/kg) and 1.6 mg/kg in preanesthetized dogs (range 0.2 – 3.5 mg/kg).

Table 29: Induction dose comparison by preanesthetic class*:

Preanesthetic	Average ALFAXAN induction dose (and range) in mg/kg	Number of dogs
No preanesthetic	2.2 (1.5-4.5)	17
Benzodiazepine + opioid + acepromazine	1.7 (0.9-3.5)	39
Opioid + acepromazine	1.6 (0.6-3.5)	80
Alpha$_2$-agonist	1.1 (0.21-2.00)	9

*see Table 27 for specific types of preanesthetics

The ALFAXAN induction dose in the field study was reduced by 23-50%, depending on the preanesthetic (dose sparing effect). Dose sparing of ALFAXAN depends on the potency, dose, and time of administration of the various preanesthetics used prior to induction.

ALFAXAN Maintenance: Maintenance doses were recorded for 60 dogs, including 17 unpreanesthetized dogs, and 43 dogs that received preanesthetics.

Table 30: Number of maintenance boluses

Number of boluses	Unpre-anesthetized	Preanesthetized	Total
1	2	6	8
2	5	7	12
3	3	9	12
4	4	4	8
5	2	6	8
6	0	5	5
7	1	4	5
11	0	1	1
23	0	1	1
Total	17	43	60

Forty-eight (of 60) dogs were maintained using between 1-5 ALFAXAN boluses. Average maintenance doses ranged between 1.3 – 2.4 mg/kg in unpreanesthetized dogs and 1.2 – 1.4 mg/kg in preanesthetized dogs. Doses were given to effect and titrated against the response of the individual patient. Mean maintenance dose (mg/kg) and number of boluses administered are summarized for dogs receiving up to 5 boluses:

Table 31a: ALFAXAN maintenance boluses & mean total dose of each bolus (mg/kg) in unpreanesthetized cats

# boluses	# dogs	mean	SD	min	max
1	17	2.2	1.30	0.5	6.0
2	15	2.2	1.23	0.3	4.1
3	10	1.5	0.52	0.6	2.1
4	7	1.3	0.62	0.5	2.1
5	3	2.4	1.62	0.9	4.1

Table 31b: ALFAXAN maintenance boluses & mean total dose of each bolus (mg/kg) in preanesthetized cats

#boluses	# dogs	mean	SD	min	max
1	43	1.2	0.86	0.2	3.4
2	37	1.4	1.30	0.1	6.8
3	30	1.3	1.04	0.2	4.0
4	21	1.2	1.12	0.3	5.1
5	17	1.2	1.40	0.3	5.9

Depending on dose, rate of administration, and frequency of maintenance bolus injections, maintenance boluses provide an additional 6 - 8 minutes of anesthesia in preanesthetized or unpreanesthetized dogs.

Inhalant Maintenance: Following ALFAXAN induction, 28 (of 118) dogs were maintained using halothane and 89 (of 118) were maintained using isoflurane. Inhalant concentration (%) was recorded at 5-10 minute intervals. Average concentrations were similar among the various preanesthetic groups and no incompatibilities were noted relating to the use of either inhalant when ALFAXAN was used for induction.

4) Apnea:

Immediate Post-induction Apnea: All dogs were intubated and received supplemental oxygen. Of 182 cases treated with ALFAXAN, information on the occurrence and duration of apnea during induction was recorded for 137 cases; data on apnea were missing for 45 cases.

Post-induction apnea (≥ 30 seconds) was recorded in 46 (of 123) preanesthetized dogs and in 9 (of 14) unpreanesthetized dogs. Apnea lasted ≥ 60 seconds in 26 of the 46 preanesthetized dogs, and in 8 of the 9 unpreanesthetized dogs. No particular preanesthetic was more or less likely to result in apnea after ALFAXAN induction.

Maintenance Apnea: Twenty-two (of 182) dogs experienced apnea during the maintenance anesthesia; 5 of these dogs were maintained using an inhalant anesthetic. Seventeen (of 64) dogs experienced apnea during ALFAXAN maintenance anesthesia (11 were preanesthetized; 6 were unpreanesthetized).

The duration of apnea was recorded for 11 of the 17 apneic dogs. These 11 dogs experienced a total of 14 periods of apnea averaging 2.55 minutes (2.63 minutes for 6 preanesthetized dogs; 2.44 minutes for 5 unpreanesthetized dogs).

5) *Induction Quality:* Induction scores were acceptable (scored highest) in >90% of the dogs.

6) *Anesthetic Quality:* Quality of anesthesia scores follow:

Table 32: Anesthesia scores and numbers of dogs

Score	# unpreanesthetized dogs	#preanesthetized dogs
1 (un-acceptable)	0	3
2 (acceptable)	1	29
3 (excellent)	16	133
Totals	17	165

Anesthesia duration varied depending on the procedure, lasting between 12 to 109 minutes in the ALFAXAN maintained dogs, and between 22 to 130 minutes in dogs maintained using an inhalant anesthetic. Of the 3 dogs that scored 'unacceptable' for anesthesia quality, all were satisfactorily induced with ALFAXAN, and 2 were maintained using inhalant anesthesia. The unacceptable anesthesia score for the dog maintained with ALFAXAN was related to the occurrence of apnea.

7) *Recovery Times:* Recovery times were evaluated as the time between extubation and head lift, and the time between extubation and sternal recumbency, and the time between extubation and standing.

Time to Head Lift: The mean time to head lift ranged between 1.5 and 21.5 minutes across treatment groups.

Table 33: Extubation to head lift (minutes) by treatment group*

	Group 1	Group 2	Group 3	Group 4
Number of dogs	17	44	28	90
Mean	21.54	14.79	1.48	4.60

*Group 1 did not receive a preanesthetic; groups 1 and 2 received ALFAXAN maintenance anesthesia; group 3 dogs were maintained using halothane; group 4 dogs were maintained using isoflurane.

Time to Sternal Recumbency: The mean time to sternal recumbency ranged between 9.6 and 30 minutes across treatment groups.

Table 34: Extubation to sternal recumbency (minutes) by treatment group*

	Group 1	Group 2	Group 3	Group 4
Number of dogs	17	43	27	90
Mean	30.00	25.36	9.57	11.88

*Group 1 did not receive a preanesthetic; groups 1 and 2 received ALFAXAN maintenance anesthesia; group 3 dogs were maintained using halothane; group 4 dogs were maintained using isoflurane.

Time to Standing: The mean time to standing ranged between 23 and 61 minutes across treatment groups.

Table 35: Extubation to standing without aid (minutes) by treatment group*

	Group 1	Group 2	Group 3	Group 4
Number of dogs	17	35	24	83
Mean	47.63	60.90	22.91	29.54

*Group 1 did not receive a preanesthetic; groups 1 and 2 received ALFAXAN maintenance anesthesia; group 3 dogs were maintained using halothane; group 4 dogs were maintained using isoflurane.

Average recovery times following ALFAXAN maintenance anesthesia were longer compared to recovery times following the use of an inhalant anesthetic.

8) *Recovery Score (quality of recovery):* Unpreanesthetized dogs had the highest percentage of poor or fair recovery scores.

Table 36: Recovery Score: Number of dogs assessed at each score level

	Group 1*	Group 2	Group 3	Group 4
1 (Poor)	2	2	0	6
2 (Fair)	4	6	3	11
3 (Good)	3	13	7	25
4 (Excellent)	8	24	17	48
Missing	0	2	1	0
Total	17	47	28	90
% scores = 1 or 2	35.3	17.8	11.1	18.9
% scores = 3 or 4	64.7	82.2	88.9	81.1

*unpreanesthetized

Physiological Data (see Adverse Reaction table below):

9) *Indirect Systolic Blood Pressure (mmHg)*: Systolic blood pressure (SBP) was evaluated using Doppler and pneumatic cuff technology. The SBP of dogs maintained with ALFAXAN remained similar to baseline values; dogs maintained with inhalants showed SBP decreases of 20 - 35 mmHg. During anesthetic recovery, SBP were similar to baseline or slightly increased. Hypertension (defined as >165 mmHg) was recorded at least once in 54 dogs and hypotension (defined as ≤70 mmHg) was recorded at least once in 32 dogs.

10) *Heart Rate (beats per minute)*: Mean heart rate (HR) increased immediately after induction in all treatment groups. During maintenance anesthesia and early recovery with inhalants, the average HR in dogs maintained with inhalants decreased compared to dogs maintained with ALFAXAN. Bradycardia (≤ 70 beats/minute) occurred at least once in 24 dogs and tachycardia (defined as ≥ 180 beats per minute) occurred at least once in 49 dogs. Bradycardia was treated successfully with atropine in 2 dogs treated with ALFAXAN. Cardiac function remained stable and clinically acceptable across dogs in all treatment groups.

11) Respiratory Rate (breaths per minute): Mean respiratory rates (RR) in all groups decreased immediately after induction to approximately 50% of baseline, remaining unchanged during maintenance. Bradypnea (RR <10 breaths/minute) occurred at least once in 89 dogs.

12) Rectal Temperature: The average rectal body temperature before anesthesia ranged between 38 - 39°C; during recovery, temperatures ranged between 36.5- 37°C. External heat sources were used to prevent extreme decreases in core body temperature during anesthesia and recovery. Hypothermia (defined as <97 °F or <36 °C) occurred in 28 of the dogs. No temperatures indicating hyperthermia were recorded.

13) Oxygen Saturation of Hemoglobin (SpO_2%): Hypoxia (SpO_2 <85%) occurred in 4 dogs during the study.

14) Mucosa color: Mucosal color remained stable across dogs in all treatment groups.

g. Adverse Reactions: The following table illustrates the number of dogs displaying each adverse reaction during the field study. Many adverse reactions reflect the physiological effects associated with general anesthesia.

Table 37: Adverse Reactions in Dog Field Study

Adverse Reaction	Number of Dogs [a] (total of 182)
Bradypnea (RR < 10 breaths/min)	89
Apnea (≥ 30 seconds)	55 (of 137)
Hypertension (> 165 mmHg)	54
Tachycardia (≥ 180 bpm)	49
Apnea (≥ 60 seconds)	34 (of 137)
Hypotension (≤ 70 mmHg)	32
Hypothermia (< 97 °F)	28
Bradycardia (≤ 70 beats/min)	24
Hypoxia (SpO_2 < 85%)	4
Unacceptable Anesthesia Quality	1
Emesis	1

[a] Each dog may have experienced more than one adverse reaction

Additional adverse reactions for dogs included vocalization, paddling, and muscle tremors.

h. Conclusions: This study confirmed the clinical effectiveness and safety of ALFAXAN when administered to dogs as the sole anesthetic agent for the induction and maintenance of anesthesia, when used in conjunction with commonly used preanesthetic agents, and when administered for induction of anesthesia with subsequent maintenance by inhalant anesthetics.

IV. TARGET ANIMAL SAFETY: CATS

A. Preanesthetic Compatibility Study

a. Title (Study No.): The cardiovascular and respiratory safety of ALFAXAN when administered IV to cats which have been premedicated with acepromazine, medetomidine, midazolam or butorphanol. (JX9604.07-H002)

b. Type of study: Preanesthetic interaction safety study

c. Study Director: Michael A. Schnell, DVM, MBA
Doylestown, PA

d. Study Design:

1) Purpose: The purpose of this study was: i) to evaluate dose sparing when ALFAXAN was administered intravenously to cats given acepromazine, medetomidine, midazolam, or butorphanol and, ii) to evaluate the interaction between ALFAXAN and the individual preanesthetics and their effects on cardiovascular and respiratory parameters when administered to cats at clinically relevant doses.

2) Description of Test Animals: Thirty adult cats (15 intact males, 15 intact females), weighing 2.5 – 7.9 kg and 2.1- 9.3 years of age, were enrolled.

3) Treatment Groups: Three female and three male cats allocated into each of five groups for treatment as follows.

Table 38: Treatment groups by preanesthetic and preanesthetic dose

Group	Preanesthetic (IM)	Preanesthetic Dose
1	0.9% saline	0.1 mL/kg
2	acepromazine	1.1 mg/kg
3	medetomidine	100 mcg/kg
4	midazolam	0.1 mg/kg
5	butorphanol	0.4 mg/kg

4) Dosage Form: ALFAXAN (alfaxalone 10 mg/mL) Anesthetic Injectable for intravenous (IV) injection in the final market formulation.

5) Administration: Twenty-five (25) ±5 minutes after administration of the intramuscular (IM) preanesthetic, ALFAXAN was administered by slow IV injection over 60 seconds, until the cat was anesthetized, at a dose up to 5 mg/kg body weight.

6) Study Variables: Cardiorespiratory measurements included mean, systolic, and diastolic blood pressure (BP), respiratory rate (RR), heart rate (HR), heart rhythm, oxygen saturation of hemoglobin (SPO_2), electrocardiogram (ECG), and temperature (T). Anesthesia variables included onset of recumbency, onset of anesthesia, duration of anesthesia, duration of recumbency, and overall anesthesia score.

7) Statistical Methods: Descriptive statistics (means and standard deviations) were summarized for all variables.

e. Results:

Anesthetic data: The lowest induction dose was 1.5 mg/kg ALFAXAN (in the medetomidine preanesthesia group) to 3.5 mg/kg (in the saline group).

Table 39: The average induction dose of ALFAXAN, overall anesthetic score, and average duration of anesthesia by preanesthetic

Average ALFAXAN Induction Dose (mg/kg)	Preanesthetic (IM)	Average Overall Anesthetic Score (lower is better)	Average Duration of Anesthesia (min)
2.2	Medetomidine 100 mcg/kg	3	98.2
2.7	Acepromazine 1.1 mg/kg	3	36.3
2.8	Butorphanol 0.4 mg/kg	3.7	26.5
3.0	0.9% Saline	4.2	26.1
3.3	Midazolam 0.1 mg/kg	4.7	16.7

Cats given midazolam as the sole preanesthetic needed more ALFAXAN compared to the saline group. Medetomidine had the largest dose sparing effect on ALFAXAN. Durations of recovery increased with the duration of anesthesia.

Physiologic variables: Data were collected after ALFAXAN administration and at 5 minute intervals until the end of anesthesia (135 minutes maximum) for pulse rate, and at 5, 10, 15, 20 minutes and then 10 minute intervals until the end of anesthesia (130 minutes maximum) for the other physiologic variables.

Acepromazine and medetomidine decreased mean systolic blood pressure prior to dosing with ALFAXAN. Systolic blood pressure in all groups decreased immediately following dosing with ALFAXAN. Acepromazine and butorphanol produced more of a decrease in mean systolic blood pressure during anesthesia compared to the control group.

Table 40a: Systolic Blood Pressure (mmHg)

Preanesthetic Group	N	Mean	STD	MIN	MAX
Saline	6	119.4	12.64	98	135
Acepromazine	6	92.6	20.90	71	124
Medetomidine	5	122.2	32.06	102	179
Midazolam	6	114.2	21.18	89	143
Butorphanol	6	99.1	10.48	81	113

Acepromazine and medetomidine decreased mean blood pressure prior to dosing with ALFAXAN. All mean blood pressures decreased after dosing with ALFAXAN; midazolam and butorphanol produced the most decrease. Acepromazine and butorphanol produced a greater decrease after dosing with ALFAXAN compared to the control group.

Table 40b: Mean Blood Pressure (mmHg)

Preanesthetic Group	N	Mean	STD	MIN	MAX
Saline	6	101.9	14.80	76	119
Acepromazine	6	79.6	17.35	63	110
Medetomidine	5	104.3	25.01	84	148
Midazolam	6	94.0	18.16	69	120
Butorphanol	6	77.1	8.20	67	89

Acepromazine and medetomidine decreased diastolic blood pressure prior to dosing with ALFAXAN. Diastolic blood pressure in all groups decreased immediately following dosing with ALFAXAN. Acepromazine and butorphanol produced more of a decrease after dosing with ALFAXAN compared to the control group.

Table 40c: Diastolic Blood Pressure (mmHg)

Preanesthetic Group	N	Mean	STD	MIN	MAX
Saline	6	92.8	16.23	70	116
Acepromazine	6	68.2	16.75	53	99
Medetomidine	5	92.2	22.77	72	131
Midazolam	6	77.0	12.93	59	94
Butorphanol	6	66.5	6.55	54	72

Acepromazine and medetomidine produced the most profound decrease in mean pulse rates prior to dosing with ALFAXAN. All mean pulse rates decreased after dosing with ALFAXAN; medetomidine produced more of a decrease after dosing with ALFAXAN. During anesthesia, 3 cats in the medetomidine preanesthesia group developed bradycardia (bradycardia defined as < 110 bpm).

Table 40d: Pulse rate (beats/minute)

Preanesthetic Group	N	Mean	STD	MIN	MAX
Saline	6	229.2	29.73	178	206
Acepromazine	6	202.5	33.22	153	234
Medetomidine	6	121.5	12.88	103	139
Midazolam	6	209.1	26.13	173	235
Butorphanol	6	206.6	25.64	161	237

Medetomidine and butorphanol produced the largest decrease in RR prior to dosing with ALFAXAN. All mean respiratory rates decreased after dosing with ALFAXAN. Midazolam and butorphanol produced the lowest mean respiratory rates during anesthesia.

Table 40e: Respiratory rate (breaths/minute)

Preanesthetic Group	N	Mean	STD	MIN	MAX
Saline	6	38.5	8.83	29	50
Acepromazine	6	33.8	11.61	25	57
Medetomidine	6	33.0	3.44	26	36
Midazolam	6	33.7	8.39	25	48
Butorphanol	6	26.2	4.56	20	33

Mean hemoglobin saturation remained approximately the same in all groups, but tended to be low (< 92%) in all groups. All study cats breathed room air spontaneously during anesthesia.

Table 40f: Oxygen saturation of hemoglobin (%)

Preanesthetic Group	N	Mean	STD	MIN	MAX
Saline	6	90.7	2.26	89	94
Acepromazine	6	91.6	3.10	87	95
Medetomidine	6	91.2	3.90	85	95
Midazolam	6	92.4	2.10	90	96
Butorphanol	6	91.0	4.13	85	96

Mean body temperature decreased in all treatment groups. Mean temperature was lowest in the medetomidine treatment group (95.5 ºF) at 100 minutes post dosing with ALFAXAN.

Table 40g: Body temperature (ºF)

Preanesthetic Group	N	Mean	STD	MIN	MAX
Saline	6	100.53	1.74	98.9	103.8
Acepromazine	6	98.50	2.10	96.3	102.3
Medetomidine	6	99.16	1.77	96.9	101.8
Midazolam	6	99.70	1.58	97.4	101.7
Butorphanol	6	99.82	1.13	98.2	101.3

ECG: A few transient arrhythmias were noted during ALFAXAN anesthesia. In addition to the 5 cats listed in the following table, 3 cats experienced bradycardia (HR <110 bpm) after medetomidine preanesthesia.

Table 41: Cardiac arrhythmias in 5 cats noted during the compatibility study by preanesthetic and time points.

Tx Group	Preanesthetic	Rhythm Abnormality	Time point (min)
3	Medetomidine	Sinus Arrhythmia[1]	30, 40, 50, 60, 70, 80,90
3	Medetomidine	Sinus Arrhythmia	90, 100, 110, 120
3	Medetomidine	Sinus Arrhythmia	50
4	Midazolam	Single VPC	5
4	Midazolam	Single VPC[2]	prior to dosing

[1]Present prior to dosing with ALFAXAN.
[2] Present prior to dosing with ALFAXAN or midazolam.

Anesthesia Scores:
Quality of induction was scored as: 1 = excitement, vocalization, defecation or urination, cannot intubate; 2 = mild excitement, some struggling, some difficulty during intubation; and 3 = no excitement, rapidly assumes lateral recumbence, good muscular relaxation, easily intubated.

Quality of anesthesia was scored as: 1 = constant tongue flicking and head shaking, does not become laterally recumbent or assumes lateral recumbence briefly, muscle rigidity accompanied with twitching, vocalization, defecation, and responds to noise; 2 = some head movements, frequent body movement, short duration of lateral recumbence, numerous attempts to rise, some muscle tremors or twitching; and 3 = minimal movement, maintains lateral recumbence and immobilization, minimal muscle tremors or twitching, no response to noise.

Quality of recovery was scored as: 1 = prolonged struggling, unable to assume sternal recumbence or difficulty in maintaining sternal or standing position, becomes excited when assisted, prolonged paddling and swimming motion; 2 = some struggling, requires assistance to sternal recumbence or standing, responsive to external stimuli, and 3 = assumes sternal recumbence with little or no struggling, attempts to stand and walk with little or no difficulty.

Table 42*: The table summarizes quality of induction, anesthesia, recovery scores, and the number of cats (%) in each group that received each score.

	Quality Score*	Saline	Acepro-mazine	Medetomi-dine	Midazolam	Butorphanol
Induction	1					
	2	1/6 (16.7%)			4/6 (66.7%)	1/6 (16.7%)
	3	5/6 (83.3%)	6/6 (100.0%)	6/6 (100.0%)	2/6 (33.3%)	5/6 (83.3%)
Anesthesia	1					
	2	2/6 (33.3%)			1/6 (16.7%)	3/6 (50.0%)
	3	4/6 (66.7%)	6/6 (100.0%)	6/6 (100.0%)	5/6 (83.3%)	3/6 (50.0%)
Recovery	1				1/6 (16.7%)	
	2	1/5 (20.0%)			3/6 (50.0%)	3/6 (50.0%)
	3	4/5 (80.0%)	6/6 (100.0%)	5/5 (100.0%)	2/6 (33.35)	3/6 (50.0%)

*Recovery scores were not recorded for 2 cats (1 receiving saline; 1 receiving medetomidine); therefore, these 2 groups contain recovery data from 5 cats.

The overall anesthesia quality score' is the sum of quality of induction, anesthesia and recovery. The minimum and maximum overall anesthesia quality scores are 3 (poorest) and 9 (best) respectively.

Table 43: The number of cats (%) in each group receiving each **'ov**erall anesthesia score**' are summarized in the table.**

Score	**Saline**	**Acepromazine**	**Medetomidine**	**Midazolam**	**Butorphanol**
6*				1/6 (16.7%)	1/6 (16.7%)
7				3/6 (50.0%)	1/6 (16.7%)
8	3/5 (60.0%)			1/6 (16.7%)	2/6 (33.3%)
9	2/5 (40.0%)	6/6 (100.0%)	5/5 (100.0%)	1/6 (16.7%)	2/6 (33.3%)

*No cats scored <6.

The quality of anesthesia based on overall anesthetic scores was acceptable for all groups; however, the lowest scores for quality of anesthesia were seen in the midazolam preanesthesia group. It may be necessary to provide additional preanesthesia when ALFAXAN is used with benzodiazepines.

f. Conclusion:

Midazolam, butorphanol, acepromazine, and medetomidine, when used as preanesthetics, are compatible with IV ALFAXAN prior to short term anesthesia. Medetomidine may result in extended periods of anesthesia. The quality of midazolam preanesthesia, when used alone prior to ALFAXAN anesthesia, was less satisfactory compared with other preanesthetics.

B. Multidose Safety Study:

a. Title (Study No.): A target animal safety study in cats after IV administration of ALFAXAN as single repeated injections on days 0, 2 and 5 at dosages of 5, 15 and 25 mg/kg. (JX9604.07-H004)

b. Type of study: Target animal safety study

c. Study Director: Michael A. Schnell, DVM, MBA,
Doylestown, PA

d. Study Design:

1) Purpose: The purpose of this study was to evaluate the margin of safety of ALFAXAN 10 mg/mL given at 1, 3, and 5 times the approximate recommended induction dose on 3 occasions.

2) Description of Test Animals: Twenty-four (24) cats (12 male, 12 female), approximately 6.6 to 10.8 months of age and 2-6 kg in body weight, were enrolled. Twenty-two cats were considered evaluable for the study.

3) Treatment Groups: The cats were randomly assigned to one of four treatment groups in the following study design:

Table 44: Treatment groups by number, gender, and dosage

Group	# Males	# Females	Article	Dosage (mg/kg)	Frequency	Route
1	2	2	Saline	0	once daily on Days 0, 2 and 5	IV
2	3	3	ALFAXAN	5	once daily on Days 0, 2 and 5	IV
3	3	3	ALFAXAN	15	once daily on Days 0, 2 and 5	IV
4	3	3	ALFAXAN	25	once daily on Days 0, 2 and 5	IV

4) Dosage Form: ALFAXAN (alfaxalone) 10 mg/mL Anesthetic Injection, the product intended for marketing in the USA administered intravenously.

5) Study Variables: Variables included clinical observations, mortality, body weight, anesthetic observations, food consumption, injection site observations, clinical pathology, and gross and histopathology. All variables (except necropsy) were evaluated prior to, during, and after test article administration.

6) Statistical Methods: All variables were reported using descriptive statistics, such as means and standard deviations, charts and tables.

e. Results:

Clinical observations: Abnormal clinical signs observed in ALFAXAN treated animals did not appear to be related to dose and no increase in severity was noted after repeated doses.

Table 45a: Clinical observations during ALFAXAN anesthesia by dose on day 1

Dose	Adverse event description	No. of cats
5 mg/kg	Fluid in endotracheal tube 10 minutes post- dose	1
	Tonic clonic activity on recovery	1
15 mg/kg	Stopped breathing 2 minutes after intubation for > 30 seconds; ventilated due to low SpO_2; moderate amount of seromucous discharge from endotracheal tube	1
	Episodes of gasping during anesthesia	1
	Required ventilation at 5 and 10 minutes post- dose	1
25 mg/kg	Excess upper airway sounds resulted in removal of endotracheal tube	1
	Slight amount of clear liquid fluid in tube	1
	coughing during recovery	1

Table 45b: Clinical observations during ALFAXAN anesthesia by dose on day 2

Dose	Adverse event description	No. of cats
5 mg/kg	Coughing occasionally after intubation	1
	Ventilation required	1
15 mg/kg	Fluid in tube, coughing at 5, 10 and 15 minutes post-dose	1
	Ventilated at 5 minutes post-dose	1
	Coughing and mucous in endotracheal tube during recovery	1
	Poor pulse pressure	1
	Ventilation required 10 minutes post-dose (SpO2 =74%); coughing 15 minutes post-dose; topical laryngeal anesthetic applied at 20 minutes post-dose	1
	Trembling, shaking, and coughing 20 minutes post-dose	1
25 mg/kg	Coughing 50 minutes post-dose; moderate amount of seromucous fluid in endotracheal tube	1
	Required ventilation 0-5 minutes after dose; coughing, slight amount of serous fluid from endotracheal tube	1
	Increased respiratory effort and sounds after extubation; slight discharge in endotracheal tube	1

Table 45c: Clinical observations during ALFAXAN anesthesia by dose on day 3

Dose	Adverse event description	No. of cats
5 mg/kg	Coughing at 15 minutes post-dose; discharge seromucous discharge from endotracheal tube	1
	Coughing; small amount of clear liquid discharge from endotracheal tube	1
15 mg/kg	Clear liquid discharge from endotracheal tube	1
	Coughing at 45 minutes post-dose; poor pulse pressure at 5 minutes post-dose; coughing at 30	1
	Coughing at 30 and 40 minutes post-dose	1
	Required ventilation 5 minutes post-dose; occasional coughing	1
25 mg/kg	Coughing and seromucous discharge from endotracheal tube	1
	Jumped off table during recovery; trembling at 70 minutes post-dose; death (see Mortality below)	1
	Ventilated at 5 minutes post-dose; coughing	1
	Trembling during recovery	1
	Ventilation at 5 minutes post-dose	1

Mortality: One study cat in the 25 mg/kg group died on the third day of anesthesia. The cat was disoriented after extubation, became excited, and leapt from the examination table to the floor. The cat's clinical status continued to decline; it became moribund and died 7 hours after induction. Clinical signs included increased respiratory rate, fluid in trachea, prolonged somnolence, and inability to move hind legs. Bloodwork was not obtained and necropsy provided no additional information regarding the cause of death.

Heart rate (HR): There was a decrease in HR in cats in the 25 mg/kg dose group compared with cats in the 5 mg/kg and 15 mg/kg dose groups.

Table 46: The means in the following table represent the minimum HR observed over the anesthetic periods for each treatment group.

Dose	Mean Pulse Rates (bpm)
5 mg/kg	↓ from 247.7 pre-dose to 212.4 at 20 minutes post-dose
15 mg/kg	↓ from 242.0 pre-dose to 216.8 at 5 minutes post-dose
25 mg/kg	↓ from 227.6 pre-dose to 186.9 at 15 minutes post-dose

Respiratory rate (RR): In general, increasing dose decreased the respiratory rate. The lowest RR (18 breaths per minute) seen in the 15 and 25 mg/kg dose groups occurred at 50 and 5 minutes post-dose respectively. Cats in the 5 mg/kg dose group reached a minimum of 23 breaths per minute at 10 minutes post-dose.

Table 47: The means in the following table represent the minimum observed respiratory rate over 3 anesthetic periods by dose.

Dose	Mean Respiratory Rates (bpm)
5 mg/kg	↓ from 50.3 pre-dose to 23.0 at 10 minutes post-dose
15 mg/kg	↓ from 59.3 pre-dose to 18.0 at 50 minutes post-dose
25 mg/kg	↓ from 58.3 pre-dose to 18.0 at 5 minutes post-dose

Saturation of hemoglobin (SpO_2): Mean hemoglobin saturation was not dose related. The lowest mean hemoglobin concentrations for cats in both the 5 and 15 mg/kg dose groups were approximately 88%. For cats that received 25 mg/kg, the lowest was 83%.

Table 48: The means in the following table represent the minimum observed SpO_2 over the anesthetic periods by dose.

Dose	Mean Hemoglobin Saturation (%)
5 mg/kg	↓ from 93.3 pre-dose to 88.5 at 15 minutes post-dose
15 mg/kg	↓ from 93.0 pre-dose to 82.9 at 5 minutes post-dose
25 mg/kg	↓ from 93.8 pre-dose to 87.8 at 5 minutes post-dose

Apnea: During the initial 5 minutes after induction, there was 1 episode of apnea at 5 mg/kg, 6 episodes of apnea at 15 mg/kg, and 3 episodes of apnea at 25 mg/kg. Apnea was not recorded after this time point.

Blood pressure (BP): Mean systolic blood pressure decreased with increasing dose.

Table 49: The table shows the minimum mean systolic BP observed over 3 anesthetic periods by dose.

Dose	Mean Systolic Blood Pressure (mmHg)
5 mg/kg	↓ from 141.5 pre-dose to 90.5 at 5 minutes post-dose
15 mg/kg	↓ from 140.8 pre-dose to 71.2 at 10 minutes post-dose
25 mg/kg	↓ from 140.7 pre-dose to 63.2 at 5 minutes post-dose

Mean diastolic blood pressure decreased with increasing dose. The means in the following table represent the minimum observed over the anesthetic period for each treatment group.

Table 50: The table shows the minimum mean diastolic BP observed over the anesthetic periods by dose.

Dose	Mean Diastolic Blood Pressure (mmHg)
5 mg/kg	↓ from 116.3 pre-dose to 74.7 at 5 minutes post-dose
15 mg/kg	↓ from 118.1 pre-dose to 55.8 at 10 minutes post-dose
25 mg/kg	↓ from 110.3 pre-dose to 44.9 at 5 minutes post-dose

Mean blood pressure decreased but was not related to dose. The maximum decrease in mean blood pressure was seen in the 15 mg/kg dose group at 10 minutes post-dose. The means in the following table represent the minimum observed over the anesthetic period for each treatment group.

Table 51: The table shows the minimum mean BP observed over the anesthetic periods by dose.

Dose	Mean Blood Pressure (mmHg)
5 mg/kg	↓ from 129.9 pre-dose to 81.6 at 5 minutes post-dose
15 mg/kg	↓ from 130.4 pre-dose to 67.5 at 10 minutes post-dose
25 mg/kg	↓ from 126.8 pre-dose to 52.9 at 5 minutes post-dose

Anesthesia times: Except for time to onset of recumbency and time to onset of anesthesia, anesthesia event times increased with increasing dose.

Table 52: Mean times (hours: mins: secs) by treatment group:

Event	5 mg/kg	15 mg/kg	25 mg/kg
Time to Onset of Recumbency	00:19	00:13	00:13
Time to Onset of Anesthesia (intubation)	01:09	00:53	01:01
Duration of Non-Responsiveness (Toe Pinch)	05:55	21:50	39:12
Duration of Non-Responsiveness (Tail Clamp)	07:28	23:30	49:02
Duration of Anesthesia (extubation)	0:15:57	0:37:44	1:16:53
Duration of Recumbency	0:42:53	1:14:58	2:19:17

Anesthesia scores:

Table 53: Mean scores by treatment group*

Event	5 mg/kg	15 mg/kg	25 mg/kg
Quality of Induction	2.8	3.0	3.0
Quality of Anesthesia	2.4	2.6	2.8
Quality of Recovery	2.7	2.8	2.6

*subjectively scored 1 to 3 (least favorable to most favorable)

Injection sites: Placement of multiple intravenous catheters caused mild to moderate redness, swelling, and pain on palpation. Clinical and necropsy observations showed no difference between injection sites of the control and 25 mg/kg dose cats.

Clinical pathology and necropsy: No abnormalities were attributed to administration of ALFAXAN.

Food consumption: Increasing dose generally decreased food consumption.

f. Conclusions: The quality of anesthesia was acceptable with all doses except in the 1 cat that received 25 mg/kg, experienced a traumatic event during recovery, and died. Duration of anesthesia increased with increasing ALFAXAN dose. Increasing doses of ALFAXAN resulted in decreases in heart rate, respiratory rate, and blood pressure within the first 15 minutes after induction.

C. Tolerance Study

a. Title (Study No.): The cardiovascular and respiratory safety of ALFAXAN when administered IV to cats at 5, 15 and 50 mg/kg. (JX9604.07-H003)

b. Type of study: Drug tolerance study

c. Study Director: Dr. William W. Muir, DVM, PhD, DACVA, DACVECC
Columbus, OH

d. Study Design:

1) Purpose: The purpose of this study was to determine the cardiovascular and respiratory effects of ALFAXAN administered at the proposed intravenous (IV) label dose of 5 mg/kg, 15 mg/kg, and 50 mg/kg (1, 3, and 10 times the label induction dose).

2) Description of Test Animals: Eight cats (4 male, 4 female) weighing 3.7 to 5.9 kg and aged approximately 2.2 to 6.3 years were enrolled in this study.

3) Treatment Groups: All cats received each dose in escalating concentration with a washout period between each dosing. On study day 0, cats were dosed with saline and 5 and 15 mg/kg ALFAXAN with washout periods of at least 1 hour following administration of saline and a minimum of 3 hours following full recovery from ALFAXAN administration. On study day 1, cats were dosed with 50 mg/kg ALFAXAN.

4) Dosage Form: ALFAXAN (alfaxalone 10 mg/mL) Anesthetic Injection, in the final market formulation, was administered intravenously. Saline (0.9%) was used as the control.

5) Study Variables:

Most data were collected on study day -7, at 60 and 5 minutes before dosing, and post-dosing at 1, 3, 5, 10, and 15 minutes, and at 10 minute intervals from 30 minutes until sternal recumbence (maximum 460 minutes). Respiration rate (RR) data were not collected at 3 minutes post dosing, and arterial blood gases (pH, PCO_2 mm Hg, and PO_2 mm Hg) were not sampled 5 minutes before dosing or at 3 and 10 minutes post dosing.

Physiologic variables: Physiologic variables included respiration rate (RR, breaths/min); heart rate (HR, beats/min); heart rhythm; systolic, diastolic, and mean blood pressure (SAP, DAP, MAP mmHg); central venous pressure (CVP, mmHg); cardiac output (CO, L/min and mL/kg/min); temperature (ºC); and venous blood pH, PCO_2 (mmHg), and PO_2 (mmHg).

Anesthetic Variables: Data were collected for the following variables: time to onset lateral recumbence (sec), time to intubation (sec), duration of non- responsiveness to toe pinch (min), duration of anesthesia (min), and duration of recovery (min).

Data were collected for the scored categorical variables: quality of induction, anesthesia, and recovery; these scores were summed to provide an overall anesthesia quality score.

6) Statistical Methods: All cats received every dose in escalating concentrations. Therefore, randomization to dose was not needed. All variables were reported using descriptive statistics, such as means and standard deviations, charts and tables.

e. Results:

Table 54: Cardiovascular results summary

Variable	Comments
Heart Rate Arterial Blood Pressure	• Dose-related decreases after ALFAXAN • Decreases were most pronounced at the 50 mg/kg dose
Heart Rhythm	• Sinus in origin • No cardiac arrhythmias attributed to ALFAXAN
Mean Systolic Arterial BP	• Remained higher than 80 mm Hg at all times at 5 and 15 mg/kg doses
Systolic Arterial BP	• Marked decrease at 50 mg/kg dose • 5 and 15 mg/kg doses increased to baseline within 15-30 minutes
Systemic Vascular Resistance	• Decreased after 15 mg/kg and 50 mg/kg doses • Increased to baseline values within 30 to 100 minutes post dose

Table 55: Respiratory, blood pH and gases, and body temperature results summary

Variable	Comment
Respiratory Rate Minute Volume	• Decreased post-dose all groups
Tidal Volume	• Increased post-dose at 5 mg/kg and 15 mg/kg doses • Decreased for 15-30 minutes post-dose at 50 mg/kg dose
Mean Arterial PO_2	• Dose dependent decreases (< 80 mm Hg) for 15-30 minutes at 5 mg/kg dose • Most pronounced decreases at 50 mg/kg dose lasting 30-40 minutes
PCO_2	• Increased in all treated dose groups • Significant increase (> 50 mm Hg) at 50 mg/kg dose
Arterial pH	• Decrease at 50 mg/kg dose • Returned to normal within 90-100 minutes
Core Body Temperature	• Decreased proportionately with cardiovascular depression and duration of anesthesia

The 5 mg/kg IV dose produced acceptable anesthesia with transient hypoxemia (PO_2 of 80 mm Hg) and apnea. Anesthesia in the 15 mg/kg dose group was associated with a greater incidence of apnea (approximately 1 minute in duration) and hypoxemia.

Apnea occurred at all ALFAXAN doses. Respiratory depression and apnea were observed at the 5, 15, and 50 mg/kg doses. The duration of apnea generally increased with the ALFAXAN dose, occurring more often and for longer duration at 15 and 50 mg/kg. One cat experienced apnea lasting 3 minutes at 5 mg/kg. In this cat, tracheal intubation, administration of 100% oxygen, and manual artificial ventilation were needed to raise arterial PO_2 from < 60 mm Hg to > 80 mm Hg. Five cats received oxygen in at the 5 mg/kg dose, 7 received oxygen at the 15 mg/kg dose, and all cats required oxygen at the 50 mg/kg dose. Other adverse reactions at the 5 mg/kg dose included 1 cat with cyanotic mucous membranes, and 1 cat with fluid in the endotracheal tube.

Changes in cardiovascular, respiratory, pH, and blood gas values were related to dose. All cardiopulmonary variables returned to baseline values (by 15 minutes at the 5 mg/kg dose and by 30 minutes at the 15 mg/kg dose) after ALFAXAN administration. The 50 mg/kg dose produced severe cardiovascular depression, resulting in euthanasia of 5 (of 7) cats after 5 hours of anesthesia. Post mortem findings revealed pulmonary edema and irreversible cerebellar changes associated with hypoxia.

Table 56: Anesthetic data summary by dose

Anesthesia variables	5 mg/kg	15 mg/kg	50 mg/kg
Time until Lateral Recumbence (secs)	33 ± 24	20 ± 4	17 ± 3
Time until Intubation (secs)	27 ± 24	19 ± 7	21 ± 13
Duration of Non-Responsiveness to Toe Pinch (mins)	17.8 ± 9.5	54.7 ± 23.9	103.9 ± 56.2
Duration of Recovery (mins)	36.3 ± 15.6	57.9 ± 44.8	98.0 ± 111.6
Duration of Anesthesia (mins)	26 ± 10.7	82.9 ± 23.9	125.6 ± 66.2 (n=2)

Duration of anesthesia was related to dose and lasted 26, 83, and 126 minutes after doses of 5, 15, and 50 mg/kg, respectively. Average quality scores (1, 2, or 3 with 1 being the best) for induction, anesthesia, and recovery were 1.0 in the 5 mg/kg and 15 mg/kg dose groups for induction and anesthesia, and 1.0 and 1.1 for recovery in the 5 and 15 mg/kg dose, respectively. Only 2 cats recovered in the 50 mg/kg dose group.

f. Conclusion:

A 5 mg/kg intravenous dose of ALFAXAN was satisfactory for induction and recovery from anesthesia in cats. Transient respiratory depression (apnea) occurred at all doses and the duration of respiratory depression was related to dose. Excessive doses of ALFAXAN (50 mg/kg) lead to severe hypoxia and irreversible brain damage.

D. Juvenile Cat Safety Study

a. Title (Study No.): A Single Site Clinical Trial in Juvenile Cats Less than 12 weeks of Age Evaluating the Effectiveness and Safety of ALFAXAN Administered for Induction and Maintenance of Anesthesia. (JX9604.07-C011)

b. Type of study: Field study

c. Investigator: Brad O'Hagan, BVSc MACVSc
Rutherford, Australia

d. Study Design:

1) Purpose: To evaluate the clinical effectiveness and safety of IV ALFAXAN in juvenile cats < 12 weeks of age.

2) Description of test animals: Thirty four (34) juvenile cats <12 weeks of age (0.9-1.7 kg) in an Australian animal shelter were enrolled. The exact age of the juvenile cats was unknown; all enrolled juvenile cats had no permanent incisor teeth. The presence of no permanent incisor teeth was considered an indicator of being aged < 12 weeks.

3) Treatment groups: All juvenile cats were induced with IV ALFAXAN after preanesthetic administration with morphine, acepromazine, and atropine. All juvenile cats were intubated after desensitizing the larynx with topical lidocaine and received carprofen injection post-operatively for analgesia. In 25 cases, juvenile cats were maintained under anesthesia with isoflurane; 8 juvenile cats were maintained with supplemental boluses of IV ALFAXAN.

4) Dosage form: Dosage Form: ALFAXAN (alfaxalone 10 mg/mL) Anesthetic Injection, the product intended for USA marketing, was administered intravenously 'to effect' (ability to intubate).

5) Study variables: Qualitative assessments of induction, maintenance, and recovery, heart rate (HR), respiratory rate (RR), ALFAXAN dose requirements, duration of anesthesia and recovery, and adverse reactions were recorded.
For the 8 cases receiving supplemental ALFAXAN boluses for maintenance, the time to first required supplemental dose and the total dose of supplemental ALFAXAN were recorded as mg/kg/hr.

6) Statistical methods: Variables were evaluated by group using descriptive statistics, such as means and standard deviations, and charts or tables.

e. Results:

The mean dose of ALFAXAN for anesthetic induction was 4.7 mg/kg (range 3.6- 5.6 mg/kg). The mean time to the first maintenance dose of ALFAXAN was 5.5 (± 2.3) minutes and the mean anesthetic administration rate for the 8 kittens maintained with ALFAXAN was 11.1 (± 4.2) mg/kg/hr.

Anesthesia was scored as excellent, acceptable, or unacceptable. The overall anesthetic score was excellent in 25 cases and acceptable in 8 cases. Of the 8 cases maintained by ALFAXAN boluses, 3 were assessed as excellent and 5 were acceptable. Recovery (scored as excellent, good, fair, or poor) was excellent in 19 and good in 9 cats. Five cases had fair anesthetic recoveries. In the 8 cases maintained with ALFAXAN, 6 had excellent recoveries, 1 good, and 1 fair. Average time to first purposeful movement after extubation for all 34 cats was 10.5 (± 8.1) minutes.

Respiratory and pulse rates were clinically acceptable in all other cases. Apnea (defined as a cessation of breathing for greater than 30 seconds) after induction was observed in 1 cat, lasting for 73 seconds, after which the cat began to breathe spontaneously.

Rectal temperature declined by an average of 2.8° C between the pre-study examination and recovery. Only female cats received maintenance anesthesia, their surgeries were longer, and therefore, female cats had a greater decline in rectal temperature than male cats.

One cat died because its endotracheal tube was incorrectly connected to the anesthetic equipment, resulting in tension pneumothorax and pneumoperitoneum. The death was unrelated to ALFAXAN.

f. Conclusions: Thirty-three kittens were satisfactorily induced to anesthesia with ALFAXAN; 8 female kittens were satisfactorily maintained using ALFAXAN boluses.

V. TARGET ANIMAL SAFETY: DOGS

A. Preanesthetic Compatibility Study

a. Title (Study No.): The cardiovascular and respiratory safety of ALFAXAN when administered to dogs intravenously which have been premedicated with acepromazine, medetomidine, midazolam, or butorphanol. (JX9604.03-H003)

b. Type of study: Drug preanesthetic interaction safety study

c. Study Director: Dr. William W. Muir, DVM, PhD, DACVA, DACVECC
Columbus, OH

d. Study Design:

1) Purpose: The purpose of this study was: i) to evaluate dose sparing when ALFAXAN was administered intravenously to dogs given acepromazine, medetomidine, midazolam, or butorphanol and, ii) to evaluate the interaction between ALFAXAN and the individual preanesthetics and their effects on cardiovascular and respiratory parameters when administered to dogs at clinically relevant doses.

2) Description of Test Animals: Forty-eight (48) healthy Beagle dogs (24 male, 24 female), weighing 8.0-15.8 kg and 0.8-2.0 years of age, were enrolled in the study.

3) Treatment Groups: In treatment groups 1 through 7, 6 dogs (3 males and 3 females) were randomly assigned to treatment group. Data from treatment group 8 was collected post-hoc and dogs were not randomized to this treatment group. The dogs were administered various preanesthesia medications at the rates listed in the table below. A control group received saline in place of the premedicant.

Table 57: Treatment groups and preanesthetics

Group	Preanesthetic (IM)	Preanesthetic Dose
1	0.9% saline	1 mL/kg
2	acepromazine	0.05 mg/kg
3	acepromazine	0.2 mg/kg
4	acepromazine	1.1 mg/kg
5	medetomidine high dose	40.0 mcg/kg
6	medetomidine low dose	4.0 mcg/kg
7	Midazolam	0.2 mg/kg
8	butorphanol	0.2 mg/kg

4) Dosage Form: ALFAXAN (alfaxalone 10 mg/mL) Anesthetic Injection, the product intended for USA marketing, was administered intravenously.

5) Administration: Twenty-five (25) ±5 minutes after administration of the preanesthetic, ALFAXAN was administered by slow intravenous injection (over 60 seconds), until the dog was anesthetized, at a rate up to 2 mg/kg body weight.

6) Study Variables: Cardiorespiratory measurements included mean, systolic, and diastolic blood pressure (BP), respiratory rate (RR), heart rate (HR), SPO_2, and temperature (T). Anesthesia variables included onset of recumbency, onset of anesthesia, duration of non-responsiveness to noxious stimulus, duration of anesthesia, duration of recumbency, overall anesthesia score, total ALFAXAN dose, and duration of ALFAXAN dose administration.

7) Statistical Analysis: The primary variables were evaluated by group using descriptive statistics, such as means and standard deviations, and charts or tables.

e. Results

Anesthesia produced muscle relaxation and loss of responsiveness to noxious stimuli as evidenced by a total loss of muscle tone and a lack of response to noxious stimulation (toe clamp).

Cardiovascular effects:

1. Saline and midazolam did not have an effect on any cardiovascular measurements.
2. Butorphanol resulted in minimal decreases in arterial blood pressure measured 5 minutes prior to treatment with ALFAXAN, a recording that persisted during anesthesia (8 minutes). There was a moderate decrease in heart rate in the butorphanol treated dogs at the end of the anesthetic period.

3. Acepromazine resulted in relative decreases in mean and diastolic arterial blood pressure 5 minutes prior to treatment with ALFAXAN. These decreases persisted during anesthesia. There was a moderate increase in heart rate for animals preanesthetized with acepromazine (0.05 mg/kg) by the end of the anesthetic period.

4. Medetomidine produced minimal changes in arterial blood pressure. Heart rate decreased 5 minutes prior to treatment with ALFAXAN following the intramuscular administration of medetomidine and remained decreased for the duration of anesthesia.

Respiratory effects:

1. Saline, midazolam, and butorphanol groups showed mild decreases in respiratory rates after the administration of ALFAXAN.
2. Respiratory rate decreased at 5 minutes prior to ALFAXAN treatment after the administration of the two higher doses of acepromazine (0.2, 1.1 mg/kg, IM). Mean respiratory rate did not change thereafter.
3. The lower dose of medetomidine resulted in slight decreases in respiratory rate at 5 minutes prior to ALFAXAN treatment. The higher dose of medetomidine produced definitive decreases in respiratory rate at 5 minutes prior to ALFAXAN treatment; this effect persisted for the duration of anesthesia.
4. Blood oxygen saturation (SpO_2%) did not change after any treatment before the administration of ALFAXAN and decreased minimally after the administration of ALFAXAN.

Apnea was not observed during the study.

Anesthesia Data:

Table 58: The average induction dose of ALFAXAN, overall anesthetic score, and average duration of anesthesia by preanesthetic are presented in the table:

ALFAXAN Induction Dose (mg/kg)	Premedicant (IM)	Average Overall Anesthetic Score (lowest is excellent/highest is unacceptable)	Average Duration of Anesthesia (min)
1.0	Medetomidine 40 mcg/kg	3	52.4
1.2	Acepromazine 1.1 mg/kg	3	10.3
1.4	Acepromazine 0.2 mg/kg	3	10.2
1.4	Acepromazine 0.05 mg/kg	4	9.1
1.4	Butorphanol 0.2 mg/kg	4	8.0
1.6	Medetomidine 4 mcg/kg	4	7.9
1.7	0.9% Saline	4	6.9
1.8	Midazolam 0.2 mg/kg	6	6.0

Dose sparing occurred with acepromazine, medetomidine, and butorphanol. Dogs administered midazolam needed an increase in dose over the saline group. The high medetomidine and 1.1 mg/kg acepromazine groups had the largest dose sparing effect on ALFAXAN. The 0.2 mg/kg and 1.1 mg/kg acepromazine, low dose medetomidine, midazolam and butorphanol groups had mean durations of anesthesia between 7:58 and 10:17 min:sec. The high medetomidine group had a prolonged mean duration of anesthesia at 1:10:08 hr:min:sec. Durations of recovery increased with the duration of anesthesia. The mean durations of toe clamp scores also increased with the duration of anesthesia.

The quality of anesthesia based on overall anesthetic scores was acceptable for all groups; however, the least favorable scores for quality of anesthesia were seen in the midazolam preanesthesia group.

f. Conclusion:

Midazolam, butorphanol, acepromazine, and medetomidine when used as preanesthetics, are compatible with ALFAXAN administered at the recommended label dose (up to 2 mg/kg IV). High doses of medetomidine may result in extended periods of anesthesia. The quality of midazolam preanesthesia, when used alone prior to ALFAXAN anesthesia, was less satisfactory compared with other preanesthetics.

B. Multidose Safety Study

a. Title (Study No.): Eight day target animal safety study of IV ALFAXAN in dogs administered every other day. (JX9604.03-H005)

b. Type of study: Target animal safety study

c. Study Director: Michael A. Schnell, DVM, MBA
Doylestown, PA

d. Study Design:

1) Purpose: The purpose of this study was to investigate the safety of ALFAXAN injection and evaluate the margin of safety associated with the drug.

2) Description of Test Animals: Twenty-four healthy Beagle dogs (12 male, 12 female), 7 months of age, were enrolled. The average weight of males at the time of their first dose was 10.1 kg (range 6.6-12.0 kg). The average weight of females at the time of their first dose was 9.5 kg (range 7.9-11.8 kg).

3) Treatment Groups: The 24 dogs were randomly assigned to 4 treatment groups of 6 animals (3 male, 3 female) each. A control group received 0.9% saline. ALFAXAN (or saline) was administered every 48 hours (Days 1, 3, and 5) for 3 treatments at the following rates:

Table 59: Treatment Groups

Tx Group	Dosage	Number and Sex of Animals
1	Saline 1 mL/kg (0X)	3 males, 3 females
2	ALFAXAN 2 mg/kg (1X)	3 males, 3 females
3	ALFAXAN 6 mg/kg (3X)	3 males, 3 females
4	ALFAXAN 10 mg/kg (5X)	3 males, 3 females

4) Dosage Form: ALFAXAN 10 mg/mL Anesthetic Injection, the final market formulation, was administered intravenously.

5) Study Variables:

General Health - Clinical observations, mortality and general health observations, food consumption, body weights, physical examination (body temperature, thoracic auscultation, and clinical health observations), clinical pathology (hematology, chemistry, coagulation, urinalysis, and fecal exam), dose administration injection site evaluation, ECG, gross necropsy, and histopathology were conducted. Body temperature, heart rate and rhythm, indirect blood pressure, hemoglobin saturation, respiratory rate, onset and end of recumbency, onset and end of anesthesia (non-responsiveness to noxious stimuli) were also recorded.

Electrocardiogram (ECG): ECGs were recorded for leads I, II, III, avR, avL, and avF. The ECGs collected on Day -4 and Day 8 were evaluated by a board certified cardiologist. Heart rhythm was evaluated prior to dose administration and at 10 minute intervals throughout anesthesia. Just prior to dose administration, lead II

electrical activity was monitored to ensure there were no existing abnormalities. The ECG leads were then removed during induction and replaced after the dog was recumbent. During the time the animal remained anesthetized, lead II electrical activity was monitored (but not recorded) every 10 minutes.

6) Statistical Analysis:

Single Time Point Analysis – For data with continuous outcomes, analysis of variance was used to evaluate effects of gender, dose, and gender by dose under the assumption of normality. If gender by dose interaction was statistically significant ($p<0.05$) no further analysis was made. If the interaction was not significant, the main effect of dose was evaluated. If the effect was significant ($p<0.10$) then pair-wise comparisons between each of the treated and non- treated groups were made.

Repeated Measures Analysis – Data collected over time were evaluated by ANOVA appropriate for repeated measures under the assumption of normality. Data were log transformed where necessary to stabilize the residuals. Dose, gender, and time as well as all 2-way and 3-way interactions of the main effects were included as fixed effects and weight block within gender was included as a random effect. If time by dose by gender was significant ($p<0.05$), no further evaluations were conducted. If the interaction was not significant ($p>0.05$), interaction between dose by gender and dose by time were evaluated. If dose by gender interaction was significant, no further analysis was made. If the dose by time interaction was significant, pair-wise comparisons were made at each time point evaluating each treatment versus control at an unadjusted $\alpha=0.10$. If neither of the 2-way interactions were significant, the main effect of dose was evaluated using the pair-wise comparisons at each time point, evaluating each treatment versus control at an unadjusted $\alpha=0.10$.

For cardiovascular and respiratory variables, a statistical model including both day and time within day as repeated measures was used to evaluate effects of dose. Dose, study day, time within day and all 2 and 3 way interactions between these effects were included as fixed effects evaluated at $\alpha=0.05$. Random effects included weight block within gender, day by subject nested in treatment interaction and time by subject nested in treatment interaction. Interactions with dose were assessed and, if statistically significant, within time or day dose effects were evaluated by comparing all pairs of means. If no interaction was detected, dose was evaluated as described above.

e. Results:

General Physical Health Parameters: Dogs consumed normal quantities of food, had stable body weights, and normal injection sites throughout the study. There were no unscheduled deaths.

The main effect of dose was on heart rate, indirect systolic pressure, and hemoglobin saturation ($p<0.05$). Heart rate increased in the 5X group compared to the dogs in the 1X group ($p<0.05$). Systolic BP was lower in dogs in the 5X group as compared to the 1X group ($p<0.05$). Increasing the dose level decreased hemoglobin saturation with oxygen, with both the 3 and 5X groups having lower values than the 1X group ($p<0.05$).

Body temperature decreased in proportion to the dose and the length of anesthesia. The lowest rectal temperature recorded was 98.3°F. There was a dose related decrease in SpO_2, respiratory rate, and blood pressures. Mean heart rates increased with the increase in ALFAXAN dosage. Mean heart rates also increased when compared to the pre-dose heart rate at the 10-minute time point for all groups. Heart rates returned to pre-dose rates or below at the 20 minute time points for the 1X and 3X groups, and at the 30 minute time point for the 5X group. There was a decrease in the mean respiratory rates for all treatment groups when compared to the pre-dose rate and was lowest at the 10 minute time point. Mean systolic BP decreased and was lowest in all groups at the 10 minute time point for the 1X group, and at the 20 minute time point for 3X and 5X groups. Similar trends were recorded for diastolic BP and MAP. Clinical pathology abnormalities were not clinically significant in all groups; abnormal necropsy and histopathology findings were associated with injection site trauma consistent with intravenous injection and repeat catheterization. No pain on injection was reported. No abnormal cardiac arrhythmias were noted during the study (ECG observed but not recorded). Heart rhythm was recorded as normal for all dogs.

Clinical pathology tests revealed a sex by dose interaction was statistically significant for BUN and total bilirubin, however reported values for total bilirubin were in the normal range for dogs and no consistent dose effect was evident for increases in BUN. No dose effects were detected for creatinine over time. A statistically significant difference (increase) was reported in GGT between the 0 and 1X groups, however, the difference was attributed mostly to one value for an animal in the 1X group.

There were no gross or microscopic pathological findings that were considered treatment-related.

Examination of anesthetic event times showed a dose proportional treatment effect for time to onset of recumbency, duration of non-responsiveness to stimulus, duration of anesthesia, and duration of recumbency among the ALFAXAN treatment groups. All animals recovered from anesthesia uneventfully and without need for artificial support.

f. Conclusion

Based on the measurements during his study, ALFAXAN 10 mg/mL injection has an acceptable margin of safety.

C. Tolerance Study

a. Title (Study No.): The cardiovascular and respiratory safety of ALFAXAN when administered intravenously to dogs at 2, 6 and 20 mg/kg. (JX9604.03-H004).

b. Type of study: Drug tolerance study

c. Study Director: William W. Muir, DVM, PhD, DACVA, DACVECC
Columbus, OH

d. Study Design:

1) Purpose: The purpose of this study was to determine the cardiovascular and respiratory effects of ALFAXAN administered at the proposed intravenous (IV) label dose of 2 mg/kg and at 6 mg/kg and 20 mg/kg (1, 3 and 10 times the label dose).

2) Description of Test System: Eight mongrel dogs (4 male, 4 female) weighing 15.0-17.5 kg and approximately 1.2-3.7 years of age were enrolled in this study.

3) Treatment Groups: The study was a four-way crossover design randomized for sequence of dose. The experiment (Day 0) was divided into 4 phases of drug administration with each animal serving as its own control and receiving each of the 4 treatments (2, 6, and 20 mg/kg test article and 1 mL/kg placebo control). A 3 hour washout period from time of extubation separated each dosing phase of the study. The test article was administered slowly over 60 seconds.

4) Dosage Form: ALFAXAN (alfaxalone 10 mg/mL) Anesthetic Injection, the product intended for USA marketing, was administered intravenously and 0.9% saline was used as the control.

5) Study Variables:

Table 60: Variables

Pre-treatment (baseline)	For evaluation of study objectives (Primary Variables)	Other
Physical Examination	Systolic & diastolic arterial blood pressure	Time to onset of recumbency
Body Weight	Central venous pressure	Time to onset of anesthesia
Serum Biochemistry	Heart Rate	Duration of aesthesia
Hematology	ECG	Duration of response to toe clamp
Heart Rate	Cardiac Output	Body temperature
ECG	Arterial Blood Gases	
Arterial Blood Gases	Respiratory Rate	
Respiratory Rate	Tidal Flow	
Tidal Flow	Duration of apnea	
Body temperature		

6) Statistical Analysis: Descriptive statistics (means and standard deviations) included charts and tables. Variables included systolic and diastolic arterial blood pressure, central venous pressure, heart rate, cardiac output, arterial PO_2, arterial PCO_2, arterial pH, respiratory rate, tidal flow and the duration of apnea. These dependent variables were analyzed separately using analysis of variance with dose as the independent variable.

e. Results:

Hemodynamic variables: ALFAXAN administration produced:

1. Increase in heart rate in all groups.
2. Dose related decreases in arterial (systolic, diastolic and mean) pressure, mean pulmonary artery pressure and cardiac output.

The changes in the above variables were most apparent between baseline and 10 minutes after treatment and were more significant at the 3X and 10X dosages. All cardiopulmonary variables returned to within baseline values by 15 minutes (2 mg/kg) and 30 minutes (6, 20 mg/kg) after drug administration except for mean pulmonary pressure which remained decreased for over 60 minutes in dogs administered 20 mg/kg (10X group).

Temperature, respiratory, pH and blood gas parameters: ALFAXAN administration caused:

1. A decrease in core body temperature with time in all groups.
2. A decrease in respiratory rate and minute volume in all groups which was greater at higher doses.
3. A dose related decrease in PO_2 that was greatest after treatment with 20 mg/kg ALFAXAN (10X group) persisting for approximately 15 minutes.
4. A dose related increase in dogs experiencing apnea (1 to 3 minutes).
5. An increased PCO_2 after administration of 6 and 20 mg/kg doses (3X and 10X); however the values remained within clinically acceptable limits.
6. A dose related decrease in arterial pH which was greatest at 5 and 15 minutes after treatment in the 20 mg/kg (10X) dose and returned to baseline values within 50 minutes.

Quality of Anesthesia: Anesthesia was typified by excellent muscle relaxation and good to excellent loss of nociception (total loss of muscle tone and a lack of response to both mechanical toe pinch and electrical buccal and mucosal stimulation). Duration of anesthesia was dose related with higher doses producing the longest duration of anesthesia.

Table 61: Anesthetic variables: duration and quality scores

ANESTHESIA VARIABLES (minutes)	2 mg/kg	6 mg/kg	20 mg/kg
Time to Lateral Recumbency (from start of injection)	0.9 ±0.3	0.5 ±0.1	0.5 ±0.4
Time to Intubation (from start of injection)	0.7 ±1.1	0.4 ±0.4	0.6 ±1.0
Duration of anesthesia (end injection to response to noxious stimulus)	9.3 ±2.9	32 ±7.1	69.7 ±23.5
Duration of anesthesia (end injection to extubation)	9.8 ±2.4	31.4 ±6.9	75.1 ±18.9
Duration of anesthesia (end injection to sternal recumbency)	18.6 ±10.4	39.5 ±8.4	84.4 ±17.8
Induction score 1-3 (1 = excellent, 3 = unacceptable)	1.3 ±0.5	1.0 ±0.0	1.0 ±0.0
Maintenance score 1-3 (1 = excellent, 3 = unacceptable)	2.0 ±0.5	1.4 ±0.5	1.0 ±0.0
Recovery Score 1-3 (1 = excellent, 3 = unacceptable)	1.4 ±0.5	1.6 ±0.7	1.3 ±0.5

One dog exhibited several seconds of head-shaking after administration of the 2 mg/kg dose and prior to relaxation and insertion of the endotracheal tube. A short period of apnea was also encountered in one dog administered the 2 mg/kg dose.

f. Conclusions:

ALFAXAN produced satisfactory induction, anesthesia, and recovery at the recommended dose (2 mg/kg). Increased doses of ALFAXAN result in earlier onset and increased duration of anesthesia compared to the recommended 2 mg/kg dose. Higher doses can result in increases in the occurrence of apnea, and decreases in blood pressure, respiratory rate, minute volume, and blood pH. An overdose with ALFAXAN produces cardiovascular and respiratory suppression.

D. Safety of Induction for Cesarean Section

a. Title (Study No.): A Multi-Center Clinical Trial Evaluating the Effectiveness and Safety of ALFAXAN Administered to Dogs for Induction of Anesthesia Prior to Cesarean Section. (JX9604.03-C016)

b. Type of study: Effectiveness and safety evaluation in dogs anesthetized for Cesarean Section.

c. Investigators: Steven Metcalfe, BSc, BVMS (Hons) MSc, MACVSc
Applecross, WA, Australia

Amanda Hulands-Nave BVSc (Hons), MACVSc MVSt
Newcomb, VIC, Australia

Michael Bell BVSc
West Craigieburn, VIC, Australia

Christine Kidd, BVSc
Manley West, QLD, Australia

d. Study Design:

1) Purpose: This study was conducted to evaluate ALFAXAN in dogs requiring anesthesia for the purpose of cesarean section surgery.

2) Description of Test Animals: Forty-eight (48) female dogs were presented for Cesarean Section at 4 veterinary hospitals.

3) Treatment Groups: Dogs were induced with ALFAXAN and anesthesia was maintained with isoflurane.

4) Dosage Form: ALFAXAN was the final market formulation.

5) Administration: ALFAXAN was administered by slow intravenous injection, up to 2 mg/kg body weight, until the dog was anesthetized.

6) Study Variables: Qualitative assessments of quality of induction, maintenance and recovery were made as well investigating cardio-respiratory parameters, and ALFAXAN dose requirements. Survival and vigor of pups delivered by cesarean section were also recorded.

e. Results:

Induction, Maintenance and Recovery Quality: The mean dose of ALFAXAN was 1.9 mg/kg. Induction was scored as 3 (on scale of 1-3) for 98% of the dogs undergoing induction with ALFAXAN (81% scored the top score of 3 during isoflurane maintenance). Recovery quality was scored as Good or Excellent in 96% of the patients.

Cardiac and respiratory stability: No adverse reactions were associated with cardiovascular or respiratory variables (SpO_2, $ETCO_2$, respiratory and pulse rates) during anesthesia.

Adverse Events: Post-induction apnea occurred in 15% of the ALFAXAN cases.

Puppy Survival and Vigor: Puppy vigor (4 neonatal reflex categories) was scored as present in the following percentage of puppies:

1) withdrawal reflex (96%)
2) suction reflex (94%)
3) anogenital reflex (83%)

4) flexion reflex (90%)

Puppy survival rates at 24 hours after birth for ALFAXAN were 96.2%.

f. Conclusion:

Induction with ALFAXAN was satisfactory for Cesarean Section when isoflurane was used for maintenance anesthesia.

VI. HUMAN FOOD SAFETY:

This drug is intended for use in cats and dogs, which are non-food animals. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

VII. USER SAFETY:

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

HUMAN WARNINGS: Not for human use. Keep out of the reach of children. ALFAXAN should be managed to prevent the risk of diversion, through such measures as restriction of access and the use of drug accountability procedures appropriate to the clinical setting.

Exercise caution to avoid accidental self-injection. Overdose is likely to cause cardiorespiratory depression (such as hypotension, bradycardia and/or apnea). Remove the individual from the source of exposure and seek medical attention. Respiratory depression should be treated by artificial ventilation and oxygen.

Avoid contact of this product with skin, eyes, and clothes. In case of contact, eyes and skin should be liberally flushed with water for 15 minutes. Consult a physician if irritation persists. In the case of accidental human ingestion, seek medical advice immediately and show the package insert or the label to the physician.

The Material Safety Data Sheet (MSDS) contains more detailed occupational safety information.

Note to physician: This product contains an injectable anesthetic.

VIII. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 514. The data demonstrate that ALFAXAN, when used according to the label, is safe and effective for the induction and maintenance of anesthesia and for induction of anesthesia followed by maintenance with an inhalant anesthetic, in cats and dogs.

A. Marketing Status

The drug is restricted to use by or on the order of a licensed veterinarian (Rx marketing status) because veterinary expertise is necessary to administer general anesthesia to cats and dogs.

B. *Exclusivity*

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 the approval because no active ingredient of the new animal drug has previously been approved.

C. *Patent Information*

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