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TECHNICAL NOTES

Alfaxan® CIV

(alfaxalone 10 mg/mL) Intravenous injectable anesthetic for use in cats and dogs.

NADA 141-342, Approved by FDA

ALFAXAN® (Schedule: C-IV)
(alfaxalone 10 mg/mL)
Intravenous injectable anesthetic for use in cats and dogs.
CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION

ALFAXAN (alfaxalone) is a neuroactive steroid molecule with properties of a general anesthetic. Alfaxalone is chemically described as 3-α-hydroxy-5-α-pregnane-11, 20-dione, and has a molecular weight 332.5. The primary mechanism for the anesthetic action of alfaxalone is modulation of neuronal cell membrane chloride ion transport, induced by binding of alfaxalone to $GABA_A$ (gamma-aminobutyric acid) cell surface receptors.

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.

DOSAGE AND ADMINISTRATION

Administer by intravenous injection only. For induction, administer ALFAXAN over approximately 60 seconds or until clinical signs show the onset of anesthesia, titrating administration against the response of the patient. Rapid administration of ALFAXAN may be associated with an increased incidence of cardiorespiratory depression or apnea. Apnea can occur following induction or after the administration of maintenance boluses of ALFAXAN. The use of preanesthetics may reduce the ALFAXAN induction dose. The choice and the amount of phenothiazine, $alpha_2$-adrenoreceptor agonist, benzodiazepine or opioid will influence the response of the patient to an induction dose of ALFAXAN.

When using ALFAXAN, patients should be continuously monitored, and facilities for the maintenance of a patent airway, artificial ventilation, and oxygen supplementation must be immediately available.

Jurox INC
American Century Tower II
4520 Main Street Kansas City, MO 64111
Phone: +1-844-ALFAXAN
Email: info@jurox.com Website: www.jurox.com

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ALFAXAN does not contain an antimicrobial preservative. Do not use if contamination is suspected. Strict aseptic techniques must be maintained because the vehicle is capable of supporting the rapid growth of microorganisms. Failure to follow aseptic handling procedures may result in microbial contamination which may cause fever, infection/sepsis, and/or other life-threatening illness.

Once ALFAXAN has been opened, vial contents should be drawn into sterile syringes; each syringe should be prepared for single patient use only. Unused product should be discarded within 6 hours. ALFAXAN should not be mixed with other therapeutic agents prior to administration.

CATS

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). 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.

ALFAXAN Induction Dose Guidelines: CATS

Preanesthetic	Average ALFAXAN induction dose and range (mg/kg)	Number of cats
No preanesthetic	4.0 (2.2 – 9.7)	33
Opioid + phenothiazine	3.2 (1.1 – 10.8)	96
Benzodiazepine + phenothiazine	3.6 (1.5 – 7.1)	23
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 + 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 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.

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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.

DOGS

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.

ALFAXAN Induction Dose Guidelines: DOGS

Preanesthetic	Average ALFAXAN induction dose and range (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.

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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.

DRUG INTERACTIONS

No specific preanesthetic is either indicated or contraindicated with ALFAXAN. The necessity for and choice of preanesthetic is left to the discretion of the veterinarian. Preanesthetic doses may be lower than the label directions for their use as a single medication. ALFAXAN is compatible with benzodiazepines, opioids, alpha$_2$-agonists, and phenothiazines as commonly used in surgical practice.

In the field study, ALFAXAN was used safely in cats and dogs that received frequently used veterinary products, including antibiotics, anticholinergics, vaccines, steroids, and dewormers.

CONTRAINDICATIONS

ALFAXAN is contraindicated in cats and dogs with a known sensitivity to ALFAXAN or its components, or when general anesthesia and/or sedation are contraindicated.

WARNINGS

When anesthetized using ALFAXAN, patients should be continuously monitored, and facilities for the maintenance of a patent airway, artificial ventilation, and oxygen supplementation must be immediately available.

Rapid bolus administration or anesthetic overdose may cause cardiorespiratory depression, including hypotension, apnea, hypoxia, or death. Arrhythmias may occur secondary to apnea and hypoxia. In cases of anesthetic overdose, stop ALFAXAN administration and administer treatment as indicated by the patient's clinical signs. Cardiovascular depression should be treated with plasma expanders, pressor agents, anti-arrhythmic agents or other techniques as appropriate for the treatments of the clinical signs.

HUMAN WARNINGS

Not for human use. Keep out of the reach of children.

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 Safety Data Sheet (SDS) contains more detailed occupational safety information. To report adverse reactions in users or to obtain a copy of the SDS for this product call 1-844-ALFAXAN.

Note to physician: This product contains an injectable anesthetic.

Jurox INC
American Century Tower II
4520 Main Street Kansas City, MO 64111
Phone: +1-844-ALFAXAN
Email: info@jurox.com Website: www.jurox.com

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DRUG ABUSE AND DEPENDENCE

Controlled Substance: ALFAXAN contains alfaxalone, a neurosteroid anesthetic and a class IV controlled substance.

Abuse: ALFAXAN is a central nervous system depressant that acts on GABA receptor associated chloride channels, similar to the mechanism of action of Schedule IV sedatives such as benzodiazepines (diazepam and midazolam), barbiturates (phenobarbital and methohexital) and fospropofol. In a drug discrimination behavioral test in rats, the effects of ALFAXAN were recognized as similar to those of midazolam. These biochemical and behavioral data suggest that ALFAXAN has an abuse potential similar to other Schedule IV sedatives.

Physical dependence: There are no data that assess the ability of ALFAXAN to induce physical dependence. However, ALFAXAN has a mechanism of action similar to the benzodiazepines and can block the behavioral responses associated with precipitated benzodiazepine withdrawal. Therefore, it is likely that ALFAXAN can also produce physical dependence and withdrawal signs similar to that produced by the benzodiazepines.

Psychological dependence: The ability of ALFAXAN to produce psychological dependence is unknown because there are no data on the rewarding properties of the drug from animal self-administration studies or from human abuse potential studies.

PRECAUTIONS

Unpreserved formulation: ALFAXAN injection does not contain an antimicrobial preservative. Do not use if contamination is suspected. Strict aseptic techniques must be maintained because the vehicle is capable of supporting the rapid growth of microorganisms. Failure to follow aseptic handling procedures may result in microbial contamination which may cause fever, infection/sepsis, and/or other life-threatening illness. Any solution remaining in the vial following withdrawal of the required dose should be discarded. Once ALFAXAN has been opened, any unused product should be discarded within 6 hours. ALFAXAN should not be mixed with other therapeutic agents prior to administration.

Rapid arousal: Careful monitoring of the patient is necessary due to possibility of rapid arousal.

Preanesthesia: Benzodiazepines may be used safely prior to ALFAXAN in the presence of other preanesthetics (see DRUG INTERACTIONS). However, when a benzodiazepine was used as the sole preanesthetic, excitation occurred in some dogs and cats during ALFAXAN anesthesia and recovery.

Apnea: Apnea may occur following administration of an induction dose, a maintenance dose or a dose administered during the transition to inhalant maintenance anesthesia, especially with higher doses and rapid administration. Endotracheal intubation, oxygen supplementation, and intermittent positive pressure ventilation (IPPV) should be administered to treat apnea and associated hypoxemia.

Blood Pressure: The myocardial depressive effects of ALFAXAN combined with the vasodilatory effects of inhalant anesthetics can be additive, resulting in hypotension. Preanesthetics may increase the anesthesia effect of ALFAXAN and result in more pronounced changes in systolic, diastolic, and mean arterial blood pressures. Transient hypertension may occur, possibly due to elevated sympathetic activity.

Body Temperature: A decrease in body temperature occurs during ALFAXAN anesthesia unless an external heat source is provided. Supplemental heat should be provided to maintain acceptable core body temperature until full recovery.

Breeding Animals: ALFAXAN has not been evaluated in pregnant, lactating, and breeding cats. ALFAXAN crosses the placenta, and as with other general anesthetic agents, the administration of ALFAXAN may be associated with neonatal depression.

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Kittens and Puppies: ALFAXAN has not been evaluated in cats less than 4 weeks of age or in dogs less than 10 weeks of age.

Compromised or Debilitated Cats and Dogs: The administration of ALFAXAN to debilitated patients or patients with renal disease, hepatic disease, or cardiorespiratory disease has not been evaluated. Doses may need adjustment for geriatric or debilitated patients. Caution should be used in cats or dogs with cardiac, respiratory, renal or hepatic impairment, or in hypovolemic or debilitated cats and dogs, and geriatric animals.

Analgesia during anesthesia: Appropriate analgesia should be provided for painful procedures.

ADVERSE REACTIONS

Adverse Reactions in Cat Field Study	
Adverse Reaction	**Number of Cats[a] = 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 (SpO2 <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. One cat that experienced tachycardia and hypoxia during anesthesia was euthanized 3 days later due to carcinoma involving the liver, pancreas and common bile duct. The relationship of the original tachycardia during anesthesia and the carcinoma is unknown.

Adverse Reactions in Dog Field Study	
Adverse Reaction	**Number of Dogs[a] = 182**
Bradypnea (RR <10 breaths/min)	89
Apnea (≥30 seconds)	55 (of 137)
Hypertension (>165 mm Hg)	54
Tachycardia (≥180 bpm)	49
Apnea (≥60 seconds)	34 (of 137)
Hypotension (≤70 mm Hg)	32
Hypothermia (<97 °F)	28
Bradycardia (≤70 beats/min)	24
Hypoxia (SpO_2 <85%)	4
Lack of Effectiveness	3
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.

Adverse drug reactions may also be reported to the FDA/CVM at 1-888-FDA-VETS or http://www.fda.gov/AnimalVeterinary/SafetyHealth/ReportaProblem/ucm055305.htm

OVERDOSE

Rapid administration, accidental overdose, or relative overdose due to inadequate dose sparing of ALFAXAN (ALFAXAN) in the presence of preanesthetics may cause cardiopulmonary depression. Respiratory arrest (apnea) may be observed. In cases of respiratory depression, stop drug administration, establish a patent airway, and initiate assisted or controlled ventilation with pure oxygen. Cardiovascular depression should be treated with plasma expanders, pressor agents, antiarrhythmic agents or other techniques as appropriate for the observed abnormality.

CLINICAL PHARMACOLOGY

The pharmacokinetic disposition of ALFAXAN injectable solution was evaluated in healthy cats following single intravenous administration at a dose of 5 mg ALFAXAN/kg bodyweight.

Pharmacokinetic parameter values[a] for ALFAXAN following intravenous administration of 5 mg ALFAXAN/kg body weight to cats (n=8)

Parameter[a]	Mean (±SD)	Range
$T_{1/2}$ (min)	43[b]	26 – 68
V_{ss} (L/kg)	1.3 (±0.7)	0.5 – 2.2
Cl_t (mL/min/kg)	24 (±8.0)	11 – 34

a: values from best-fitting 2 or 3 compartment model
b: harmonic mean
V_{ss}: steady state volume of distribution
Cl_t: total body clearance

The pharmacokinetic disposition of ALFAXAN injectable solution was evaluated in healthy dogs following single intravenous administration at a dose of 2 mg/kg bodyweight.

Pharmacokinetic parameter values[a] for Alfaxan® following intravenous administration of 2 mg ALFAXAN/kg body weight to dogs (n=8)

Parameter[a]	Mean ±SD	Range
$T_{1/2}$ (min)	34[b]	23 – 63
V_{ss} (L/kg)	2.0 (±0.4)	1.6 – 2.7
Cl_t (mL/min/kg)	59.4 (+12.9)	38 - 79

[a]: values from best-fitting 2 or 3 compartment model
[b]: harmonic mean
V_{ss}: steady state volume of distribution
Cl_t: total body clearance

American Century Tower II
4520 Main Street Kansas City, MO 64111
Phone: +1-844-ALFAXAN
Email: info@jurox.com Website: www.jurox.com

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EFFECTIVENESS

Cat Field Study: Two hundred and seven cats of 19 breeds, between the ages of 1 month to 17 years, weighing between 0.6-9 kg, were successfully anesthetized for various types of surgery or procedures requiring anesthesia. Induction doses ranged between 1.0-10.8 mg/kg for cats that received preanesthetics, and between 2.2-9.7 mg/kg for unpreanesthetized cats (see DOSAGE AND ADMINISTRATION for doses by preanesthetic treatment groups). For most cats, the ALFAXAN induction dose was reduced (10-43%), depending on the combination of preanesthetics (dose sparing effect). One hundred and four cats were maintained using an inhalant anesthetic; 72 cats were maintained using between 1 to 5 ALFAXAN boluses. Mean ALFAXAN maintenance doses ranged between 1.1-1.3 mg/kg in preanesthetized cats and 1.4-1.5 in unpreanesthetized cats. Doses were given to effect and titrated against the response of the individual patient.

All cats in the field study were intubated and received supplemental oxygen. Apnea ≥30 seconds occurred in 28 (of 169) preanesthetized cats and 4 (of 33) unpreanesthetized cats after induction with ALFAXAN. Apnea continued ≥60 seconds in 9 of the 28 apneic preanesthetized cats and 3 of the 4 apneic unpreanesthetized cats after induction with ALFAXAN. Other adverse reactions included hypotension, tachycardia, hypertension, bradypnea, bradycardia, and hypothermia (see ADVERSE REACTIONS).

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. Average recovery times following the use of an inhalant anesthetic ranged between 1 – 95 minutes (mean 14 minutes).

Dog field study: One hundred eighty-two dogs of 54 breeds, between the ages of 3 months to 13 years, weighing between 2.4 and 41 kg, were successfully anesthetized for various types of surgery or procedures requiring anesthesia. Induction doses ranged between 0.2 – 3.5 mg/kg for preanesthetized dogs, and between 1.5 – 4.5 mg/kg for dogs that did not receive a preanesthetic (see DOSAGE AND ADMINISTRATION for doses by preanesthetic treatment groups). The ALFAXAN induction dose in the field study was reduced by 23-50% depending on the combination of preanesthetics (dose sparing effect). One hundred and eighteen dogs were maintained using an inhalant anesthetic; 17 dogs were maintained using between 1-5 ALFAXAN boluses. ALFAXAN maintenance doses ranged between 1.2 – 1.4 mg/kg in preanesthetized dogs and 1.5 – 2.2 in unpreanesthetized dogs. Doses were given to effect and titrated against the response of the individual patient.

All dogs in the field study were intubated and received supplemental oxygen. Following induction using ALFAXAN, apnea ≥30 seconds occurred in 46 (of 123) preanesthetized dogs and 9 (of 17) unpreanesthetized dogs. Apnea continued for ≥60 seconds in 18 of the 46 apneic preanesthetized dogs and 8 of the 9 apneic unpreanesthetized dogs after induction with ALFAXAN. The duration of apnea ranged between 38 seconds and 6 minutes, 47 seconds. Of the 17 dogs that received up to 5 ALFAXAN maintenance boluses, 11 (64.7%) experienced 14 periods of apnea, averaging 2.6 minutes each. Other adverse reactions included bradypnea, hypotension, tachycardia, hypertension, hypothermia, and bradycardia (see ADVERSE REACTIONS).

ANIMAL SAFETY

Cat multiple dose safety study: In a multiple dose safety study**,** 5 groups of 6 healthy cats (half male, half female) were administered ALFAXAN at 0 (saline), 5, 15 and 25 mg/kg on days 0, 2 and 5, at 48 hour intervals. Variables included induction and recovery times, heart rate (HR), respiratory rate (RR), indirect blood pressure (BP), clinical pathology, and necropsy. Anesthetic and cardiorespiratory variables were collected prior to induction and at 10 minute intervals after each induction until recumbence. Electrocardiograms (ECG) were monitored at observation time points.

Recovery time increased with increasing dose. Increasing doses of ALFAXAN resulted in decreases in heart rate, respiratory rate, and blood pressure within 15 minutes post-induction. The lowest RR (18 breaths per minute) seen at 15 and 25 mg/kg 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. 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. Decreases in mean hemoglobin saturation (SpO_2) were not dose related. The lowest mean hemoglobin concentration for cats in both the 5 and 15 mg/kg dose groups were approximately 88%. For cats that received 25 mg/kg, the lowest SpO_2 was 83%. Mean systolic and diastolic blood pressure decreased with increasing dose. No abnormal cardiac arrhythmias were noted during the study (ECG observed but not recorded). Clinical pathology abnormalities were not clinically significant for 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.

The most common adverse reactions were post-anesthetic coughing, fluid in the endotracheal tube, and increased airway sounds. One death occurred in the 25 mg/kg group due to complications associated with a traumatic fall following extubation.

Cat preanesthetic compatibility study: Thirty healthy cats (15 female and 15 male cats) were allocated to each of 5 preanesthetic treatment groups. ALFAXAN dose sparing and the cardiovascular and respiratory interaction of ALFAXAN when administered following intramuscular preanesthetic administration of acepromazine, medetomidine, midazolam, butorphanol, or saline, were evaluated. No procedures were performed; no cat received maintenance anesthesia.

Table: Preanesthetic, preanesthetic dose, ALFAXAN dose, and duration of anesthesia

Preanesthetic (IM)	Preanesthetic Dose	ALFAXAN IV Induction Dose (mg/kg)	Average Duration of Anesthesia (min)
medetomidine	100 mcg/kg	2.2	98.2
acepromazine	1.1 mg/kg	2.7	36.3
butorphanol	0.4 mg/kg	2.8	26.5
0.9% saline	0 mg/kg	3.0	26.1
midazolam	0.1 mg/kg	3.3	16.7

Cats given midazolam as the sole preanesthetic required more ALFAXAN than the saline group. Durations of recovery increased with the duration of anesthesia. Physiologic variables (HR, RR, BP, SpO_2) remained satisfactory during anesthesia and reflected the effects primarily of the associated preanesthetic. Transient cardiac arrhythmias were noted during ALFAXAN anesthesia in several cats. Three cats preanesthetized with medetomidine experienced sinus arrhythmias (1 prior to ALFAXAN) and 3 were bradycardic (HR <110 bpm). Two cats that received midazolam preanesthesia showed isolated ventricular premature contractions (VPC; 1 prior to ALFAXAN).

The quality of anesthesia based on overall anesthetic scores was acceptable for all groups. However, the quality of midazolam preanesthesia, when used alone prior to ALFAXAN anesthesia, was less satisfactory compared with other preanesthetics.

Cat tolerance safety study (1, 3, 10X induction doses): Eight adult, healthy cats (4 male and 4 female) received 0 (saline), 5, 15, and 50 mg/kg of ALFAXAN over 2 days in a dose escalation design, with at least 3 hours between doses.

Decreases in HR, RR, decreases in PaO_2, and increases in $PaCO_2$ were related to dose. All cardiopulmonary variables returned to baseline values by 15 minutes (5 mg/kg), 30 minutes (15 mg/kg) and 1 hour (50 mg/kg) after ALFAXAN administration. The 50 mg/kg dose produced marked cardiovascular depression lasting from 10 to 30 minutes. Five of seven cats dosed at 50 mg/kg were euthanized due to prolonged hypoxia after 5 hours of anesthesia.

Apnea occurred at all doses. Respiratory depression and apnea (duration averaging 21 seconds, 63 seconds and 28 minutes) were observed at the 5, 15 and 50 mg/kg doses, respectively. 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.

Tracheal intubation and administration of 100% oxygen and manual artificial ventilation were needed to raise arterial PaO_2 from < 60 mm Hg to > 80 mm Hg. Five cats received oxygen at 5 mg/kg, 7 received oxygen at 15 mg/kg, and all cats required oxygen at 50 mg/kg. Other adverse reactions at 5 mg/kg included 1 cat with cyanotic mucous membranes, and 1 cat with fluid in the endotracheal tube.

Duration of anesthesia increased with higher doses, lasting 26, 83, and 126 minutes after administration of 5, 15, and 50 mg/kg, respectively. Average quality scores (1, 2 or 3 - with 1 being the best) for induction and anesthesia were 1.0 for cats that received the 5 or 15 mg/kg doses. Average quality scores for recovery were 1.0 and 1.1 for the 5 and 15 mg/kg groups, respectively.

Dog multiple dose safety study: In a multiple dose safety study, 4 groups of 6 healthy Beagle dogs (3 male, 3 female) were administered ALFAXAN at 0 (saline), 2, 6, and 10 mg/kg, 3 times at 48 hour intervals. Variables included induction and recovery times, HR, RR, indirect BP, clinical pathology, urinalysis, and necropsy. Anesthetic and cardiorespiratory variables were collected prior to induction and at 10 minute intervals after each induction until recumbency. Health observations, clinical pathology, and urinalysis variables were collected during the study on non-treatment days.

Induction times decreased and recovery times increased with relation to the anesthetic dose. Body temperature decreased in proportion to the dose and the length of anesthesia. The minimum 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, lowest at the 10 minutes time point. Mean systolic BP decreased and was lowest in all groups at the 10 minute time point for the 1X dogs, 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).

Dog preanesthetic compatibility study: Forty eight healthy Beagle dogs (24 males, 24 females) were enrolled with 3 females and 3 males allocated to each of 8 preanesthetic groups (0.9% saline, medetomidine 40µg/kg, medetomidine 4µg/kg, acepromazine 1.1 mg/kg, acepromazine 0.2 mg/kg, acepromazine 0.05 mg/kg, butorphanol 0.2 mg/kg, and midazolam 0.2 mg/kg). All treatment groups received a maximum induction dose of 2 mg/kg of ALFAXAN (to achieve endotracheal intubation) in conjunction with an intravenous dose of differing preanesthetic according to treatment group. No procedure was performed. Data were collected on each dog for the quality of anesthesia, as well as cardiovascular and respiratory parameters. Data for the cardiovascular and respiratory variables were collected between preanesthetic administration until recovery at intervals of -60, -5, 5, 10, 15, and 20 minutes and every 10 minutes thereafter.

Dose sparing occurred with acepromazine, medetomidine, and butorphanol. Dogs administered midazolam required an increase in dose compared to 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). Duration of recovery increased with the duration of anesthesia. Midazolam treated dogs had the least satisfactory recovery scores.

No dog experienced hypotension. Mean heart rates decreased compared to baseline values. Dogs in the high medetomidine group experienced bradycardia through the end of anesthesia. Heart rates for the saline, 0.05 mg/kg acepromazine, and midazolam groups increased between the -5 minutes and 5-minute time points. The midazolam group experienced mean heart rates of 170-175 at the 5-10 minute time points. Dogs in the 0.2 mg/kg and 1.1 mg/kg acepromazine group, and butorphanol group had stable heart

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rates from baseline, premedication, and through anesthesia. Electrocardiogram recordings were evaluated by the study investigator, and no abnormal findings were noted. Blood pressures were obtained by an indirect method and remained normal in all groups throughout anesthesia. Respiratory rates decreased in the high and low medetomidine groups after premedication (-5 minutes) and again after ALFAXAN administration (5 minutes). Decreases for the other groups occurred after ALFAXAN administration, and had not returned to baseline values at the last recorded time point. No apnea was observed.

Dog tolerance safety study (1, 3, 10X induction doses): Eight dogs (4 male, 4 female) each received 0 (0.9% saline), 2, 6, and 20 mg/kg of ALFAXAN in sequence, with a 3 hour washout period between doses. There were no unscheduled deaths during the study. Necropsy and histopathology were not conducted. ALFAXAN produced dose related decreases in cardiovascular, respiratory, pH, and blood gas values, and dose related increases for duration of anesthesia, time to extubation, and time to sternal recumbency. There were no ECG abnormalities reported during the study. Observations during anesthesia included forelimb rigidity and shivering/shaking during recovery, paddling, excitement during recovery, inability to intubate (1X).

Apnea occurred in a dose dependent manner, and all dogs required oxygen supplementation and positive pressure ventilation after administration of the 10X dose. One dog experienced apnea after administration of the 1X dose, and 6 dogs experienced apnea after the 3X dose. These dogs did not require oxygen supplementation. The mean duration of apnea also increased in a dose related manner. Decreases in respiratory rate were most profound at 1 through 10 minutes in the 3X group, and 1 through 30 minutes in the 10X group. Tidal volume and minute volume decreased in a dose dependent manner, along with the respiratory rate.

Blood pressures were obtained from an arterial catheter. At all doses, there was an increase in the mean heart rate, compared to baseline values. At the 10X dose, the heart rate returned to near baseline values between the 5 and 15 minute time points. At 10X, the heart rates were tachycardic (means 155 – 168 bpm); at the 1X and 3X doses the heart rates were elevated (means 143-150 bpm). At the 1X and 3X doses, the MAP and systolic BP increased compared to baseline, and at the 10X dose, the MAP and systolic BP decreased compared to baseline. These changes occurred at 1 and 5 minutes at the 1X dose, and at 1 minute for the 3X dose. The mean MAP and systolic BP returned to baseline values by the end of anesthesia. Cardiac output (CO) and central venous pressure (CVP) were lowest in the 10X group at 5 and 30 minutes.

Dog cesarean section safety study: Forty-eight female dogs received ALFAXAN for induction prior to cesarean section, and were maintained using isoflurane. The average induction dose of ALFAXAN was 1.9 mg/kg. Immediate, transient, post-induction apnea occurred in 15% of cases. Cardiovascular and respiratory parameters were well maintained during induction, maintenance and recovery, and anesthesia quality was scored as good during all phases. Puppy vigor scores were rated as very good for withdrawal reflex, sucking reflex, anogenital reflex, and flexion reflex. Puppy survival rate was 96.2% at 24 hours after birth.

STORAGE INFORMATION

Store at controlled room temperature 15-30°C (59-86°F). Protect from freezing. Once ALFAXAN has been opened, vial contents should be drawn into sterile syringes; each syringe should be prepared for single patient use only. Unused product should be discarded within 6 hours.

HOW SUPPLIED

ALFAXAN is supplied in 10 mL single-use vials containing 10 mg ALFAXAN per mL.

Manufactured in Australia by Jurox Pty Limited

Distributed by:

Jurox Inc.
4520 Main Street
Kansas City, MO 64111
Phone 1-844-ALFAXAN