

Date of Approval: June 6, 2018

FREEDOM OF INFORMATION SUMMARY
SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-342

Alfaxan[®] Multidose

(alfaxalone)

Injectable Solution

Cats and Dogs

The effect of the supplement provides for the addition of preservatives to the formulation and use of a multidose vial

Sponsored by:

Jurox Pty. Ltd.

Table of Contents

I.	GENERAL INFORMATION	3
II.	EFFECTIVENESS	7
	A. Dosage Characterization	7
	B. Substantial Evidence	7
III.	TARGET ANIMAL SAFETY.....	17
	A. Cat Safety Studies	18
	B. Dog Safety Study	22
IV.	HUMAN FOOD SAFETY	24
V.	USER SAFETY	24
VI.	AGENCY CONCLUSIONS.....	25
	A. Marketing Status.....	25
	B. Exclusivity.....	25
	C. Supplemental Applications.....	25
	D. Patent Information	25

I. GENERAL INFORMATION

A. File Number

NADA 141-342

B. Sponsor

Jurox Pty. Ltd.
85 Gardiner St.
Rutherford, NSW 2320
Australia

Drug Labeler Code: 049480

U.S. Agent:
James H. Schafer, DVM
Schafer Veterinary Consultants, LLC
800 Helena Court
Fort Collins, CO 80524

C. Proprietary Name

Alfaxan® Multidose

D. Product Established Name

Alfaxalone

E. Drug Enforcement Agency (DEA) Schedule

Alfaxan® Multidose (alfaxalone) is a neuroactive steroid molecule with properties of a general anesthetic and is a Class IV controlled substance.

F. Pharmacological Category

Anesthetic; DEA Schedule Class IV (CIV) controlled substance

G. Dosage Form

Injectable solution

H. Amount of Active Ingredient

10 mg/mL

I. How Supplied

10 and 20 mL vials

J. Dispensing Status

Rx

K. Dosage Regimen

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 - 10.8 mg/kg for cats that received a preanesthetic. The alfaxalone induction dose in the field study was reduced by 10 - 43%, depending on the combination of preanesthetics (dose sparing effect). Dose sparing of Alfaxan® Multidose 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® Multidose 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. Draw up the maximum expected target dose and administer to effect. The actual induction dose should be based on patient response.

Alfaxalone Induction Dose Guidelines: CATS

Preanesthetic	Average alfaxalone induction dose and range (mg/kg)	Number of cats
No preanesthetic	4 (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)	26
Alpha ₂ -adrenergic agonist with/without phenothiazine	3.6 (1.1 - 5)	15
Alpha ₂ -adrenergic agonist + phenothiazine with/without benzodiazepine or opioid	2.9 (1 - 3.9)	11

Additional doses of Alfaxan® Multidose 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® Multidose and intubation, anesthesia may be maintained using intermittent Alfaxan® Multidose 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® Multidose 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.

Alfaxalone 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 alfaxalone 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® Multidose, 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 alfaxalone induction dose in the field study was reduced by 23 - 50% depending on the combination of preanesthetics (dose sparing effect). Dose sparing of Alfaxan® Multidose 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® Multidose against the response of the patient. In the field study, the use of a preanesthetic appeared to decrease the occurrence of apnea following alfaxalone induction in dogs.

In dogs, Alfaxan® Multidose 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. Draw up the maximum expected target dose and administer to effect. The actual induction dose should be based on patient response.

Alfaxalone Induction Dose Guidelines: DOGS

Preanesthetic	Average alfaxalone 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)	9

Additional doses of Alfaxan® Multidose 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® Multidose and intubation, anesthesia may be maintained using intermittent Alfaxan® Multidose 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® Multidose 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.

Alfaxalone Maintenance Dose Guidelines: DOGS

Dose and Duration	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 alfaxalone 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® Multidose, similar to a maintenance dose, may be required to facilitate the transition to inhalant maintenance anesthesia.

L. Route of Administration

Intravenous

M. Species/Class

Cats and Dogs

N. Indication

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

O. Effect of Supplement

This supplement provides for the addition of preservatives to the formulation and use of a multidose vial.

II. EFFECTIVENESS

A. Dosage Characterization

The dosage range for the preserved Alfaxan[®] Multidose formulation is the same as the previously approved dosage range of the unpreserved Alfaxan[®] formulation. The Freedom of Information (FOI) Summary for the original approval of NADA 141-342, dated September 6, 2012, contains dosage characterization information for the use of alfaxalone in cats and dogs.

B. Substantial Evidence

Additional effectiveness studies were not conducted to support the approval of the preserved alfaxalone formulation (Alfaxan[®] Multidose), because bioequivalence was demonstrated between Alfaxan[®] and Alfaxan[®] Multidose. In addition, during the bioequivalence study the monitoring of physiological variables, evaluation of anesthetic induction, anesthetic effectiveness, anesthetic recovery, and anesthetic event times showed that the two formulations result in similar pharmacodynamic effects further supporting the effectiveness and safety of the preserved formulation. The FOI Summary for the original approval of NADA 141-342, dated September 6, 2012, contains a summary of studies that demonstrate effectiveness of alfaxalone for the induction and maintenance of anesthesia and for induction of anesthesia followed by maintenance with an inhalant anesthetic, in cats and dogs.

1. Cat Bioequivalence Study

Title: An *in vivo* study investigating the bioequivalence of Alfaxan[®] versus alfaxalone plus preservatives as an injectable anesthetic agent in cats (Study No. JX9604.08-L024).

Study Dates: September - October 2013

Study Locations:

Ontario, CANADA
Rutherford, NSW, AUSTRALIA

Study Design:

Objective: One objective of this study was to demonstrate the bioequivalence of the unpreserved formulation Alfaxan[®] (alfaxalone + 2-hydroxypropyl- β -cyclodextrin – the Control Article) to a formulation of Alfaxan[®] containing the preservatives benzethonium chloride and chlorocresol, and co-solvent ethanol (Alfaxan[®] Multidose – the Test Article) when administered for the purpose of

inducing general anesthesia in the cat. Another objective of the study was to support the effectiveness and safety of Alfaxan® Multidose in cats by demonstrating comparable pharmacodynamic effects of the 2 formulations. This study was conducted in accordance with Good Laboratory Practices.

Study Animals: Twenty-four (12 male/12 female) healthy, adult cats of mixed breed weighing 3 to 6 kg and approximately 10 months to 3 years of age.

Experimental Design: Randomized, two period, cross-over with a 7-day washout period between each treatment administration (see table II.1).

Table II.1: Treatment Groups in Cat Bioequivalence Studies

Treatment Group	n	Sequence	Period 1	Washout	Period 2
1	6M, 6F	A (Alfaxan® Multidose – Alfaxan®)	Alfaxan® Multidose (Test)	7 Days	Alfaxan® (Control)
2	6M, 6F	B (Alfaxan® – Alfaxan® Multidose)	Alfaxan® (Control)	7 Days	Alfaxan® Multidose (Test)

Inclusion Criteria: Cats that were determined to be healthy based on physical examination and clinical pathology results prior to study initiation.

Exclusion Criteria: Cats that were pregnant or lactating, abnormal clinical pathology findings, cats that would not tolerate handling during the study, cats that received anesthetics, analgesics or corticosteroids after Day -7.

Drug Administration: Each cat was administered Test or Control Article through a cephalic vein catheter at 5 mg alfaxalone/kg body weight (BW) over a period of 60 seconds. The point dose proposed for the evaluation of bioequivalence is the approximate effective dose expected to achieve induction of the 90th percentile of patients, and reflects the dosage recommendations contained on the approved Alfaxan® labeling (NADA 141-342).

Measurements and Observations:

- Daily observations
- Cats were subjected to a physical examination by a veterinarian on Day -7 and on each day of treatment prior to Test or Control Article administration.
- Cats were weighed using a calibrated scale on Day -1 and on the morning of each treatment day.
- Once anesthetized, 0.1 mL of 2% lidocaine was applied to the larynx to facilitate intubation. The cat was intubated and laid in lateral recumbency on an electric warming blanket and attached to a modified Jackson-Rees non re-breathing circuit with 100% medical grade oxygen. A capnograph to measure end-tidal carbon dioxide (ETCO₂) and pulse oximeter to

measure oxygen saturation of hemoglobin (SpO₂) were placed on the cat immediately afterward.

- The first post-treatment pharmacokinetic (PK) blood sample was collected 2 minutes (± 1 minute) after the end of alfaxalone administration. Remaining blood samples for PK analysis of alfaxalone were collected at 5, 10, 20 (± 1 min); 30, 45, 60 (± 3 min); and 120, 240, 480, and 720 (± 5 min) minutes after the end of Test or Control Article administration. Plasma was harvested from blood samples and analyzed for alfaxalone using a validated High Performance Liquid Chromatography method with tandem Mass Spectrometric detection (HPLC- MS/MS).
- Pre-treatment pulse rate, heart rate and rhythm, respiratory rate, and mucous membrane color were recorded. Study personnel observed each cat continuously and recorded the following parameters at 5 minute intervals until removal of the endotracheal tube: pulse rate, heart rate and rhythm (auscultated), respiratory rate, SpO₂, ETCO₂, and mucous membrane color.
- Rectal temperature was recorded immediately before treatment and every 10 minutes after treatment until the cat was in sternal recumbency (cats were on warming blankets during anesthesia).
- The time at which the following events occurred was recorded: start of Test or Control article administration, end of Test or Control article administration, first breath after completion of Test or Control article administration, endotracheal tube placement, endotracheal tube removal, head lift, sternal recumbency, and unassisted standing.
- Subjective quality assessments of anesthetic induction, effectiveness, and recovery were performed by a Board Certified Veterinary Anesthesiologist (BCVA) using a visual analogue scale (VAS). The BCVA was masked to treatment group.

Statistical Methods:

Non-compartmental pharmacokinetic analyses were performed using the WinNonlin software (version 6.3, Pharsight Corp., CA, USA). The area under the plasma concentration versus time curve from time 0 to the last quantifiable time point (AUC_{last}) for each cat was calculated using the linear trapezoidal method. The maximum plasma concentration (C_{max}) for each cat was the highest observed concentration. The C_{max} and AUC_{last} were logarithmically transformed prior to bioequivalence analysis. The statistical model included sex, sequence, period, formulation, sex-by-sequence, sex-by-period and sex-by-formulation as fixed effects and subject nested within sequence-by-sex as a random effect. For two products to be bioequivalent, the back-transformed lower and upper bounds of the 90% confidence limits of difference between means of the test and control are contained within the acceptable limits of 80%-125% for both C_{max} and AUC_{last}.

Analysis of variance was used to evaluate all continuous variables. Models included sex, sequence, formulation, period, sex-by-sequence, sex-by-period, and sex-by-formulation as fixed effects. Animal within sequence-by-sex was

included as a random effect. For variable measured more than once throughout the study, the following fixed effects were also included: time and the interactions treatment-by-time, sequence-by-time and period-by-time as fixed effect. If pre-treatment values existed, the value closest to the first treatment administration was included as a covariate. VAS data were analyzed and evaluated as described above for bioequivalence.

For normally distributed variables observed at multiple time points within a period, a repeated measures ANOVA (RMANOVA) or a repeated measures analysis of covariance (RMANCOVA) where time 0 values were available, was used to evaluate the results associated with formulation (the MIXED procedure in SAS). The statistical model included sex, sequence, period, formulation, time, sex-by-sequence, sex-by-period, sex-by-formulation and all interactions with time as fixed effects. Animal within sequence-by-sex was included as a random effect. Period and time were modelled as repeated measures and a compound symmetric structure was assumed for each of the associated covariance matrices. Time points for the analysis were included as available.

For variables that were not normally distributed, appropriate distributional assumptions and link functions were employed using generalized linear mixed model analysis (the GLIMMIX procedure in SAS) using the same models described previously for normally distributed variables. For all models described, the baseline value was included as a covariate when applicable. VAS data were analyzed and evaluated as described above for bioequivalence.

Results:

All cats survived the study. Cats maintained their body weight and were healthy throughout the entire study period. There was no observed pain upon injection or injection site reactions for either the Test or Control Article. All physiological variables observed after the induction of anesthesia were within clinically acceptable limits for both Test and Control Article. All anesthetic times and the quality of anesthesia (induction, recovery, and overall anesthesia) were scored similarly between the 2 formulations.

Clinical observations did not reveal any differences between alfaxalone formulations. Heart rates (HR) were similar between the 2 formulations. Respiratory rates (RR) were more variable throughout the study (compared to HR) for both formulations. For the 10 minute timepoint, RR for Alfaxan® Multidose was significantly increased compared to Alfaxan® ($p < 0.10$). The difference was not clinically relevant.

RR did not return to preanesthesia levels by the final timepoint for all cats. No cats showed RR that were considered low (bradypnea) during anesthesia (range of 5 to 41 breaths/minute).

Body temperatures were similar throughout the study between the two formulations; however, during anesthesia, temperatures were artificially maintained (warming blanket). ETCO₂ levels were similar between unpreserved alfaxalone and preserved alfaxalone during the study (all cats received 100% oxygen). Capillary refill times (CRTs) were consistently 1 - 2 seconds and mucous membranes (MM) were recorded as 'pink' for all cats at

all timepoints during the study for both formulations.

Anesthetic Induction, Effectiveness, and Recovery were scored using a subjective visual analogue scale (VAS; 1 - 100; worst to best). Overall anesthesia and induction scores were similar between the 2 formulations. Recovery scores for these unpreanesthetized, healthy cats showed more variability and less satisfactory (lower) recovery scores in both groups. Recovery following alfaxalone is generally smoother when animals are preanesthetized. Sixteen cats scored ≤ 50 during recovery. Neither anesthetic consistently scored 'better' compared to the other.

Most cats were intubated between 1 - 3 minutes and were extubated at similar times between the 2 treatment groups (ranging from 12 - 34 minutes). Head lift times were extremely variable among cats, ranging from 4 - 42 minutes (averaging at 19 minutes). Shorter or longer times were not associated with either formulation. Times to sternal recumbency were similar with both formulations averaging approximately 26 minutes. Average time to standing was 41 minutes (ranging between 22 - 98 minutes) with neither formulation being consistently longer or shorter compared to the other.

In summary, the pharmacodynamic variables measured during this bioequivalence study did not differ in a clinically significant manner between the 2 formulations.

For plasma alfaxalone concentration versus time data, the lower and upper bounds of the 90% confidence intervals for C_{max} and AUC_{last} of Alfaxan[®] and Alfaxan[®] Multidose met the bioequivalence criteria of 80-125%.

Table II.2: Summary of Bioequivalence Parameters Following a Single IV Administration of 5 mg/kg in Cats of Alfaxan[®] (unpreserved) and Alfaxan[®] Multidose

Parameter	Alfaxan [®] (unpreserved) Geo LSMean [†]	Alfaxan [®] Multidose Geo LSMean [†]	T/R*	Lower Bound [‡]	Upper Bound [‡]
C_{max} ($\mu\text{g/mL}$)	8.45	8.18	0.97	91.89%	102.98%
AUC_{last} ($\text{min} \cdot \mu\text{g/mL}$)	186.07	182.01	0.98	93.79%	102.95%

* T/R= Test/Reference = Alfaxan[®] Multidose / Alfaxan[®] (unpreserved)

† Geometric least squares mean

‡ Lower and upper 90% confidence bounds for the ratio of Alfaxan[®] (unpreserved) and Alfaxan[®] Multidose

Statistical analysis of the pharmacodynamics data including physiological variables, anesthetic event times, and VAS for quality of anesthesia showed:

1. There was a statistically significant formulation-by-time interaction for respiratory rate ($P < 0.10$). At 10 minutes following the completion of dosing, respiratory rates were significantly lower in cats dosed with

Alfaxan[®] compared to cats dosed with Alfaxan[®] Multidose (18 vs. 21 breaths/min, respectively). However, this was not clinically relevant.

2. No other physiological variables or anesthetic event times differed statistically between formulations.
3. The sex-by-formulation interaction was statistically significant ($p < 0.10$) for anesthetic effectiveness as evaluated by VAS, thus within sex bioequivalence was evaluated for this outcome. The confidence interval for the difference between the two drugs, relative to the Alfaxan[®] mean value was -17.57% (lower) and 1.20% (upper) in females and 0.83% (lower) and 19.23% (upper) in males. All of these values fell within the acceptance region of $\pm 20\%$. Therefore, the drugs were deemed bioequivalent based on anesthetic effectiveness scoring.
4. For VAS, none of the model effects were statistically significant for induction or recovery VAS; therefore, Alfaxan[®] and Alfaxan[®] Multidose were similar based on anesthetic and recovery scores.

Adverse Reactions: No adverse reactions were observed during the study.

Conclusions: The results of the study demonstrate that Alfaxan[®] Multidose is bioequivalent to Alfaxan[®] in the cat when administered intravenously at 5 mg/kg. Monitoring of physiological variables, evaluation of anesthetic induction, anesthetic effectiveness, anesthetic recovery, and anesthetic event times demonstrated that the two formulations result in similar pharmacodynamic effects. Bioequivalence and clinical safety results support the safety and effectiveness of Alfaxan[®] Multidose in cats when administered at the labeled dose and for the labeled indications.

2. Dog Bioequivalence Study

Title: An *in vivo* study investigating the bioequivalence of Alfaxan[®] versus alfaxalone plus preservatives as an injectable anesthetic agent in dogs (Study No. JX9604.08-L026).

Study Dates: October-November 2013

Study Locations:

Ontario, Canada
Rutherford, NSW, Australia

Study Design:

Objective: The objective of this study was to demonstrate the bioequivalence of the unpreserved approved Alfaxan[®] formulation to a formulation of alfaxalone containing the preservatives benzethonium chloride and chlorocresol, and co-solvent ethanol (Alfaxan[®] Multidose) when administered for inducing general anesthesia in the dog. Another objective of the study was to support the effectiveness and safety of Alfaxan[®] Multidose in dogs by demonstrating comparable pharmacodynamic effects of the 2 formulations. This study was conducted in accordance with Good Laboratory Practices.

Study Animals: Twenty-four (24), healthy, adult, male Beagle dogs weighing 7.8 to 10.5 kg.

Experimental Design: A randomized, two-treatment, two-period, crossover with a 7-day washout period between each treatment administration (see Table II.3).

Table II.3: Treatment Groups in Dog Bioequivalence Studies

Treatment Group	n	Sequence	Period 1	Washout	Period 2
1	12M	A (Alfaxan [®] Multidose – Alfaxan [®])	Alfaxan [®] Multidose (Test)	7 Days	Alfaxan [®] (Reference)
2	12M	B (Alfaxan [®] – Alfaxan [®] Multidose)	Alfaxan [®] (Reference)	7 Days	Alfaxan [®] Multidose (Test)

Drug Administration: Each dog was administered Test or Control Article through a cephalic vein catheter at 3 mg alfaxalone/kg BW over a period of 60 seconds. The point dose proposed for the evaluation of bioequivalence is the approximate effective dose expected to achieve induction of the 90th percentile of patients, and reflects the dosage recommendations contained on the approved Alfaxan[®] labeling (NADA 141-342).

Inclusion Criteria: Dogs were determined to be healthy based on physical examination and clinical pathology results prior to study initiation.

Exclusion Criteria: Dogs that were pregnant or lactating, abnormal clinical pathology findings, dogs that would not tolerate handling during the study, dogs that received anesthetics, analgesics or corticosteroids after Day -7.

Measurements and Observations:

- Daily observations.
- Dogs were subjected to a physical examination by a veterinarian on Day -7 or -6, and on each day of treatment prior to Test or Control Article administration.
- Dogs were weighed using a calibrated scale on Day -1 and on the morning of each treatment day.
- Once anesthetized, the dog was intubated and laid in lateral recumbency on an electric warming blanket and attached to a Universal F circuit with 100% medical grade oxygen. A capnograph to measure end-tidal carbon dioxide (ETCO₂) and pulse oximeter to measure oxygen saturation of hemoglobin (SpO₂) were placed on the dog immediately afterward.
- The first post-treatment pharmacokinetic (PK) blood sample was collected (2 minutes [\pm 1 min] after the end of drug administration). Remaining

blood samples for PK analysis of alfaxalone were collected at 5, 10, 20 (\pm 1 min); 30, 45, 60 (\pm 3 min); and 120, 240, and 480 (\pm 5 min) minutes after the end of Test or Control Article administration. Plasma was harvested from blood samples and analyzed for alfaxalone using a validated High Performance Liquid Chromatography method with tandem Mass Spectrometric detection (HPLC- MS/MS).

- Pre-treatment pulse rate, heart rate and rhythm, respiratory rate, and mucous membrane color were recorded. Study personnel observed each dog continuously and recorded the following parameters at 5 minute intervals until removal of the endotracheal tube: Pulse rate, heart rate and rhythm, respiratory rate, SpO₂, ETCO₂, and mucous membrane color.
- Rectal temperature was recorded immediately before treatment and every 10 minutes after treatment until the dog was in sternal recumbency.
- The time at which the following events occurred was recorded: Start of Test or Control Article administration, End of Test or Control Article administration, First breath after completion of Test or Control Article administration, Endotracheal tube placement, Endotracheal tube removal, Head lift, Sternal recumbency, and Unassisted standing.
- Subjective quality assessments of anesthetic induction, effectiveness, and recovery were performed by a Board Certified Veterinary Anesthesiologist (BCVA) using a visual analogue scale (VAS). The BCVA was masked to treatment group.

Statistical Methods:

Non-compartmental pharmacokinetic analyses were performed using the WinNonlin software (version 6.3, Pharsight Corp., CA, USA). The area under the plasma concentration versus time curve from time 0 to the last quantifiable time point (AUC last) for each dog was calculated using the linear trapezoidal method. The maximum plasma concentration (C_{max}) for each dog was the highest observed concentration. The C_{max} and AUC_{last} for each dog were logarithmically transformed prior to bioequivalence analysis. The statistical model included sequence, period, and formulation and subject nested within sequence as a random effect. For two products to be bioequivalent, the back transformed lower and upper bounds of the 90% confidence limits of difference between means of the test and control are contained within the acceptable limits of 80%-125% for both C_{max} and AUC_{last}.

Analysis of variance was used to evaluate all continuous variables. Models included sequence, formulation, and period as fixed effects. Animal within sequence was included as a random effect. For variables measured more than once throughout the study, the following fixed effects were also included: time and the interactions treatment-by-time, sequence-by-time, and period-by-time. If pre-treatment values existed, the value closest to the first treatment administration was included as a covariate. VAS data were analyzed and evaluated as described above for bioequivalence.

Results:

All dogs survived the study. Dogs maintained their body weight and were healthy throughout the entire study period. There was no observed pain upon injection or injection site reactions for either the Test or Control Article. All physiological variables observed after the induction of anesthesia were within clinically acceptable limits for both formulations.

Abnormal clinical observations were limited to hypersalivation (2 dogs) and transient scleritis (2 dogs); the abnormal observations were not associated with a particular formulation.

Heart rates were similar between the two formulations. There was a significant ($p=0.072$) treatment effect for pulse rate (femoral) but not for heart rate (auscultated). This statistical difference was not clinically relevant. RRs were more variable compared to HR, and similar between the 2 formulations. Capillary refill time (CRT), mucous membrane color (MM), peripheral capillary oxygen saturation (SpO_2), and end tidal carbon dioxide ($ETCO_2$) were normal for both formulations in these healthy dogs that were supplemented with oxygen during anesthesia. Dogs' temperatures were maintained artificially during anesthesia (electric warming blanket); no hypothermia was observed during the study.

Anesthetic Induction, Effectiveness, and Recovery were scored using a visual analogue scale (VAS; 1 - 100; worst to best). Anesthetic scores for induction averaged 89 (range 70 - 94). Overall anesthesia quality scores were similar to induction scores (average 87; range 83 - 93). Recovery scores were the lowest (average 80; range 69 - 91). Sixteen dogs scored <80. Neither formulation scored 'better' compared to the other.

All dogs were intubated within approximately 2 minutes and swallowing began between 5 - 9 minutes after drug administration (extubation). Extubation times were neither longer nor shorter for either formulation. Time to head lift varied greatly among dogs, ranging from 1.75 to 20.8 minutes but did not correlate with either formulation. The duration for time until full standing recovery ranged from 8.8 to 37.6 minutes, with neither formulation showing consistently longer or shorter anesthetic duration.

In summary, clinical data confirmed that Alfaxan[®] and Alfaxan[®] Multidose are pharmacodynamically similar.

For plasma alfaxalone concentration over time data, the lower and upper bounds of the 90% confidence intervals for C_{max} and AUC_{last} of Alfaxan[®] and Alfaxan[®] Multidose met the bioequivalence criteria of 80 - 125%.

Table II.4: Summary of Bioequivalence Parameters Following a Single IV Administration of 3 mg/kg in Dogs of Alfaxan® (unpreserved) and Alfaxan® Multidose

Parameter	Alfaxan® (unpreserved) Geo LSMean†	Alfaxan® Multidose Geo LSMean†	T/R*	Lower Bound‡	Upper Bound‡
C _{max} (µg/mL)	4.42	4.74	1.07	100.26%	114.57%
AUC _{last} (min*µg/mL)	74.77	78.92	1.06	101.52%	109.72%

* T/R= Test/Reference = Alfaxan® Multidose/ Alfaxan® (unpreserved)

† Geometric least squares mean

‡ Lower and upper 90% confidence bounds for the ratio of Alfaxan® (unpreserved) and Alfaxan® Multidose

Statistical analysis of the pharmacodynamics data including physiological variables, anesthetic event times, and VAS for quality of anesthesia showed:

1. Dogs had statistically significantly different (p=0.072) pulse rates following Alfaxan® Multidose compared to those administered Alfaxan® (175 vs. 164 beats/min, respectively). This difference was not deemed clinically relevant.
2. No other physiological variables or anesthetic event time differed statistically between treatment groups.
3. For VAS, none of the model effects were statistically significant for induction, effectiveness, or recovery VAS; therefore, Alfaxan® and Alfaxan® Multidose were deemed bioequivalent based on anesthetic induction, effectiveness, and recovery scores.

Adverse Reactions: The following adverse reactions were observed in the study. None of the events were attributed to the Test or Control Article:

One dog was noted to have moderate hypersalivation on Day 1, the morning after dosing with Alfaxan®. This clinical sign resolved without need for medical intervention. Hypersalivation was also observed in this dog during Day -6 observations (without anesthesia).

One dog was noted to have mild scleritis in the right eye on Day 3 (3 days after treatment with the Alfaxan®). This clinical sign resolved without need for medical intervention. No other observations of scleritis were made for this dog.

One dog was noted to have mild bilateral scleritis on Day 6 (6 days after treatment with Alfaxan® Multidose). This clinical sign resolved without need for medical intervention. No other observations of scleritis were made for this dog.

Conclusions: The results of this study demonstrate that Alfaxan® Multidose is bioequivalent to Alfaxan® in the dog when administered intravenously at

3 mg/kg. Monitoring of physiological variables, evaluation of anesthetic induction, anesthetic effectiveness, anesthetic recovery, and anesthetic event times demonstrated that the two formulations result in similar pharmacodynamic effects. This study supports the safety and effectiveness of Alfaxan® Multidose in dogs when administered at the labeled dose and for the labeled indications.

III. TARGET ANIMAL SAFETY

The results of the bioequivalence studies demonstrate that Alfaxan® Multidose is bioequivalent to Alfaxan® in the dog when administered intravenously (IV) at 3 mg/kg and in the cat when administered IV at 5 mg/kg (see EFFECTIVENESS). During the studies, monitoring of physiological variables, evaluation of anesthetic induction, anesthetic effectiveness, anesthetic recovery, and anesthetic event times showed that the two formulations result in similar pharmacodynamic effects, which supports the safety of the preserved formulation. In addition, the following studies support the safety of IV administration of preserved formulations of alfaxalone.

Two clinical safety studies in cats and one clinical safety study in dogs were conducted with non-final formulations of preserved alfaxalone (Table III.1). The non-final formulations were almost identical to the Alfaxan® Multidose final formulation, and the minor differences in the preservative concentrations were not expected to affect safety. For comparison, the Alfaxan® Multidose final formulation contains the following co-solvent and preservatives: Ethanol 150 mg/mL (15%), Chlorocresol 1 mg/mL (0.1%), and Benzethonium chloride 0.2 mg/mL (0.02%).

Table III.1: Study Number, Title, and Formulation Evaluated the Clinical Safety Studies in Cats and Dogs

Study No.	Species	Title	Preservative System
JX9604.08-K014	Cat	The comparative safety and efficacy of Alfaxan® plus preservatives with Alfaxan® at a dose rate of 5 mg alfaxalone/kg body weight as an intravenous anesthetic induction agent in cats.	Ethanol (15%) Chlorocresol (0.15%) Benzethonium chloride (0.02%)
JX9604.08-K016	Cat	The comparative safety and efficacy of preserved alfaxalone compared to Alfaxan® anesthetic injection administered repeatedly at 5 mg alfaxalone/kg intravenously to achieve at least one hour duration of anesthesia in the cat.	Ethanol (15%) Chlorocresol (0.12%)

Study No.	Species	Title	Preservative System
JX9604.08-K013	Dog	The comparative safety and efficacy of alfaxalone plus preservatives compared to unpreserved Alfaxan® at a dose rate of 2 mg/kg as an intravenous anesthetic induction agent in dogs.	Ethanol (15%) Chlorocresol (0.15%) Benzethonium chloride (0.02%)

A. Cat Safety Studies

1. Cat Anesthesia Induction Study

Title: The comparative safety and efficacy of Alfaxan® plus preservatives versus Alfaxan®, at a dose rate of 5 mg alfaxalone/kg body weight as an intravenous anesthetic induction agent in cats (Study number JX9604.08-K014).

Study Dates: June 2012

Study Location: High Range, NSW, Australia

Study Design:

Objective: The objective of this study was to determine whether the addition of preservatives to Alfaxan® Anesthetic Injection had any effect on safety variables and the duration and/or quality of anesthesia produced in cats when administered without premedication.

Study Animals: Twelve cats (9 male and 3 female) were selected for the study. The cats were healthy, mixed gender, domestic short hair, between 7 months and 8 years old, and weighing between 3.2 and 8.2 kg.

Experimental Design: The experimental design was a randomized, 2 period, crossover with 7 days of washout between treatments.

Drug Administration: Each cat was administered alfaxalone at a dose rate of 5 mg/kg (average label induction dose), using either the preserved or unpreserved formulation.

Measurements and Observations: On each day of treatment administration the cats were weighed and received a physical examination by a veterinarian. Each cat was observed continuously and the following parameters were recorded during anesthesia at 5 minute intervals: pulse rate, heart rate, respiratory rate, SpO₂%, end-tidal partial pressure of carbon dioxide (ETCO₂), mucous membrane color, and indirect blood pressure (BP). Rectal temperature was recorded every 10 minutes. Quality of anesthesia was assessed by the same masked study individual using a Visual Analogue Scale (VAS). The times of induction, anesthesia, and recovery were recorded.

Statistical Methods:

Analysis of variance was used to evaluate all continuous variables. Models included sequence, formulation, and period as fixed effects. Animal within sequence was included as a random effect. For variables measured more than once throughout the study, the following fixed effects were also included: time and the interactions treatment-by-time, sequence-by-time, and period-by-time. If pre-treatment values existed, the value closest to the first treatment administration was included as a covariate. The difference between treatment groups was evaluated at $\alpha = 0.10$.

VAS data were analyzed and evaluated with a 90% confidence interval of the difference between Alfaxan® and the preserved alfaxalone formulation (relative to the mean value for Alfaxan®) and standard acceptance criteria of $\pm 20\%$. The statistical model included sequence, period, and group formulation and the random effect was subject nested within sequence as a random effect.

Results:

Anesthesia was induced and endotracheal intubation was successful in all cats using both preserved and unpreserved formulations. Physiological variables were similar between formulations and remained within clinically acceptable ranges for stable cardiorespiratory function during anesthesia.

Preserved alfaxalone showed no additional safety concerns, either locally (i.e. pain during injection) or systemically compared to Alfaxan®. Preserved alfaxalone produced short term anesthesia within 60 seconds that was similar to Alfaxan® in terms of quality and duration of anesthesia.

Indirect systolic blood pressure (SAP) was higher following administration of preserved alfaxalone; however, no cat showed hypertension and the difference was not clinically significant. SpO₂ was lower with preserved alfaxalone; however, no cat was hypoxemic (SpO₂ following both products ranged between 92 – 98%) and the difference was not clinically significant.

Plasma concentrations were comparable during the elimination phase (45 – 105 minutes) following administration of both formulations.

Conclusion: Anesthesia induced in unpremedicated cats with the preserved alfaxalone formulation was comparable to anesthesia induced with the unpreserved reference product, Alfaxan®, following IV administration of a single dose of 5 mg/kg over 60 seconds. Clinical and physiological results were similar between the two alfaxalone formulations. Anesthesia quality, as well as anesthetic induction, anesthesia, and recovery times revealed no additional safety concerns specifically associated with the preserved alfaxalone formulation.

2. Cat Anesthesia Induction and Maintenance Study

Title: The Comparative Safety and Efficacy of Preserved Alfaxalone Compared to Alfaxan® Anesthetic Injection Administered Repeatedly at 5 mg Alfaxalone/kg Intravenously to Achieve at Least One Hour Duration of Anesthesia in the Cat (Study number JX9604.08-K016).

Study Dates: November - December 2012

Study Locations: High Range, NSW, Australia

Study Design:

Objective: The objective of this study was to determine whether the addition of preservatives to unpreserved Alfaxan® had any effect on the safety or quality of anesthesia in cats when used to induce and maintain anesthesia using repeated bolus intravenous injections for at least 60 minutes.

Study Animals: Six cats (5 male and 1 female) were used during the study. The cats were healthy, domestic short hair, between 1-8 years old, weighing between 3.5 and 5.8 kg.

Experimental Design: The experimental design was a randomized, 2 period, crossover with 7 days of washout between treatments.

Drug Administration: Each cat was administered alfaxalone at a dose rate of 5 mg/kg (average label induction dose), using either the preserved or unpreserved formulation. Cats were administered additional doses of 5 mg/kg, as needed to maintain anesthesia for the 60 minute duration.

Measurements and Observations: On each day of treatment administration the cats were weighed and received a physical examination by a veterinarian. Cats were unpremedicated, received alfaxalone IV over 60 seconds, and were intubated. All cats were kept on warming blankets and received IV fluids during anesthesia.

Anesthetic monitoring included pulse oximeter to measure oxygen saturation of hemoglobin (SpO₂), capnograph to measure end-tidal carbon dioxide (ETCO₂), non-invasive blood pressure (BP), electrocardiogram (ECG), and HR and RR were recorded every 5 minutes. Mucous membrane color (MM) and capillary refill time (CRT) were also recorded every 5 minutes; rectal temperature (T) every 10 minutes. Every 5 minutes a noxious stimulus (toe pinch) was applied. When a positive response was noted, a repeat bolus dose of alfaxalone (5 mg alfaxalone/kg) was administered over 60 seconds. HR, RR, and BP were assessed before the noxious stimulus or the insertion of a rectal thermometer. Quality of anesthesia was scored subjectively by a masked individual with experience in feline anesthesia using a Visual Analogue Scale (VAS) scoring system. Anesthetic variables were recorded, including time of intubation, time of extubation, time to head lift, time to sternal recumbency, and time of each repeat bolus dose administration.

Clinical pathology: Venous blood and manually expressed urine samples were collected from each cat on the day before treatment, on recovery from anesthesia (after extubation), and approximately 24 hours following treatment. Blood and urine were analyzed for hematology, serum biochemistry, coagulation profile, and urinalysis.

Statistical Methods:

Analysis of variance was used to evaluate all continuous variables. Models included sequence, formulation, and period as fixed effects. Animal within sequence was included as a random effect. For variables measured more than once throughout the study, the following fixed effects were also included: time and the interactions treatment-by-time, sequence-by-time, and period-by-time. If pre-treatment values existed, the value closest to the first treatment administration was included as a covariate. The difference between treatment groups was evaluated at $\alpha = 0.10$.

VAS data were analyzed and evaluated with a 90% confidence interval of the difference between Alfaxan® and the preserved formulation (relative to the mean value for Alfaxan®) and standard acceptance criteria of $\pm 20\%$. The statistical model included sequence, period, and group formulation and the random effect was subject nested within sequence as a random effect.

Results:

The addition of preservatives did not impact the clinical performance of alfaxalone. No concerns were noted during injection and there were no mortalities.

Maintenance anesthesia (3 doses, up to 60 minutes) in cats was similar between the 2 formulations, even when the elevated average induction dose of 5 mg/kg was used for each maintenance injection (approved maintenance dose is approximately 1 - 2 mg/kg). The mean total dose of alfaxalone (n = 6) administered to induce and maintain anesthesia for at least 60 minutes was similar between formulations (18.3 \pm 2.6 mg/kg Alfaxan®, and 18.3 \pm 5.2 mg/kg preserved alfaxalone).

The first maintenance dose was administered after a mean of 13.16 minutes from induction (Alfaxan®; n = 6) and 13.94 minutes (preserved alfaxalone, n=6). The second maintenance dose was administered after a mean of 29.39 minutes from induction (Alfaxan®, n=6) and 29.16 minutes (preserved alfaxalone, n=5). The third maintenance dose was administered after a mean of 48.21 minutes (Alfaxan®, n=4) and 42.57 minutes (preserved alfaxalone, n=4). One cat received a fourth maintenance dose of preserved alfaxalone, at 50.5 minutes.

Anesthetic times (time to onset, duration of anesthesia, and recovery) and quality were similar between the 2 formulations.

Anesthesia was physiologically similar between the 2 formulations for HR, RR, SpO₂, ETCO₂, ECG, indirect BP, rectal temperature, mucosal color, and CRT.

No period of post-induction apnea occurred, and no apnea was observed following repeat doses with either formulation.

The clinical pathology results were unremarkable and results were similar between the two formulations.

Conclusion: Anesthesia produced and maintained for at least 60 minutes in unmedicated cats with repeat IV bolus doses of 5 mg/kg preserved

alfaxalone was comparable with anesthesia resulting from the use of Alfaxan[®]. Based on the results (clinical, physiological, anesthetic, and clinical pathology), no additional safety concerns are specifically associated with the preserved alfaxalone formulation in cats. The use of 5 mg/kg as the maintenance dose provided additional safety information at elevated maintenance dose levels.

B. Dog Safety Study

1. Dog Anesthesia Induction Study

Study Title: The comparative safety and efficacy of alfaxalone plus preservatives compared to unpreserved Alfaxan[®], at a dose of 2 mg/kg as an intravenous anesthetic induction agent in dogs (Study number JX9604.08-K013).

Study Dates: April - May 2012

Study Locations: High Range, NSW, Australia

Study Design:

Objective: The objective of this study was to determine whether the addition of preservatives to unpreserved Alfaxan[®] had any effect on the safety or quality of anesthesia in dogs when used to induce anesthesia.

Study Animals: Twelve adult, healthy dogs were used during the study. Dogs had an average body weight of 18 kg (range 12.6 – 22.4 kg).

Experimental Design: The experimental design was a randomized, 2 period, crossover with 6 days of washout between treatments.

Drug Administration: Each dog was administered alfaxalone intravenously at a dose rate of 2 mg/kg over a period of 60 seconds, using either the preserved or unpreserved formulation.

Measurements and Observations: On each day of treatment administration the dogs were weighed and received a physical examination by a veterinarian. The quality of anesthesia was assessed by a masked individual using a Visual Analogue Scale. Each dog was observed until it could stand and walk unaided. The times of induction, anesthesia, and recovery were recorded. No maintenance anesthesia was conducted in dogs. General health observations were recorded 6 and 24 hours after anesthetic administration.

Physiological variables were recorded at 5 minute intervals following induction of anesthesia, including pulse rate (PR), heart rate (HR), respiratory rate (RR), oxygen percent saturation of hemoglobin (SpO₂), end-tidal carbon dioxide (ETCO₂), mucous membrane color, and indirect blood pressure (BP).

Statistical Methods:

Analysis of variance was used to evaluate all continuous variables. Models included sequence, formulation, and period as fixed effects. Animal within sequence was included as a random effect. For variables measured more than

once throughout the study, the following fixed effects were also included: time and the interactions treatment-by-time, sequence-by-time, and period-by-time. If pre-treatment values existed, the value closest to the first treatment administration was included as a covariate. The difference between treatment groups was evaluated at $\alpha = 0.10$.

VAS data were analyzed and evaluated with a 90% confidence interval of the difference between Alfaxan[®] and the preserved formulation (relative to the mean value for Alfaxan[®]) and standard acceptance criteria of $\pm 20\%$. The statistical model included sequence, period, and group formulation and the random effect was subject nested within sequence as a random effect.

Results:

Endotracheal intubation was successfully completed in all dogs with a dose rate of 2 mg/kg, using either Alfaxan[®] or preserved alfaxalone. For 20 (of 24) dogs, the duration of anesthesia lasted less than 10 minutes resulting in a single physiological evaluation at the 5 minute timepoint. Heart and pulse rate were higher following preserved alfaxalone, but the increases were not clinically significant. In all dogs, SpO₂ was within an acceptable physiological range (92 – 98%) for anesthetized dogs breathing 100% oxygen. In all dogs, ETCO₂ was within the physiological range for anesthetized dogs (39-48 mmHg), indicating that respiratory function was satisfactory for removal of carbon dioxide from the body following administration of both anesthetics. In all dogs, indirect blood pressure was observed to be within clinically acceptable limits. Indirect systolic (SAP) and mean (MAP) BP remained greater than 80 and 60 mmHg, indicating that perfusion of vital organs was adequate. Most dogs (20 of 24) showed a decrease in rectal temperature. Four dogs showed a mild increase in rectal temperature (0.1 – 0.5°C) during anesthesia with preserved alfaxalone, compared to a slight increase in 1 dog that received Alfaxan[®]. No pain upon injection was observed after administration of preserved alfaxalone.

The pharmacodynamic effects of Alfaxan[®] and preserved alfaxalone were similar when given IV to 24 dogs over 60 seconds after a single dose of 2 mg/kg. Plasma alfaxalone concentrations were similar throughout the study (3 measurements).

One dog failed to become anesthetized on initial administration of preserved alfaxalone. The dog was subsequently anesthetized with Alfaxan[®] 6 days later. Two weeks after the study the dog was successfully anesthetized using preserved alfaxalone.

Conclusion: Anesthesia induced in unpremedicated dogs was comparable to anesthesia induced with the unpreserved reference product, Alfaxan[®], following IV administration of a single dose of 2 mg/kg over 60 seconds. Clinical and physiological results were similar between the two alfaxalone formulations. Anesthesia quality, as well as anesthetic induction, anesthesia, and recovery times revealed no additional safety concerns specifically associated with the preserved alfaxalone formulation.

IV. HUMAN FOOD SAFETY

This drug is intended for use in cats and dogs. 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.

V. USER SAFETY

CVM did not require user safety studies for this approval.

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

WARNINGS:

Human Safety: Not for human use. Keep out of the reach of children.

Alfaxan® Multidose 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 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.

DRUG ABUSE AND DEPENDENCE:

Controlled Substance: Alfaxan® Multidose contains alfaxalone, a neurosteroid anesthetic that is a class IV controlled substance.

Abuse: Alfaxalone 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 alfaxalone were recognized as similar to those of midazolam. These biochemical and behavioral data suggest that alfaxalone has an abuse potential similar to other Schedule IV sedatives.

Physical dependence: There are no data that assess the ability of alfaxalone to induce physical dependence. However, alfaxalone 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 alfaxalone can also produce physical dependence and withdrawal signs similar to that produced by the benzodiazepines.

Psychological dependence: The ability of alfaxalone 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.

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data demonstrate that Alfaxan[®] Multidose 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

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to properly administer the injection, and to monitor the safe use of the product, including treatment of any adverse reactions.

B. Exclusivity

This supplemental approval for Alfaxan[®] Multidose qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the FD&C Act because the supplemental application included safety studies. This exclusivity begins as of the date of our approval letter and only applies to the addition of preservatives to the formulation and use of a multidose vial.

C. Supplemental Applications

This supplemental NADA did not require a reevaluation of the safety or effectiveness data in the original NADA (21 CFR 514.106(b)(1)).

D. Patent Information

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