Date of Approval: August 1, 2014

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-342

ALFAXAN

Alfaxalone
10 mg/mL Intravenous injectable anesthetic
Cats and Dogs

The effect of the supplement provides for the approval of the revised labeling components to reflect the placement of alfaxalone into Schedule IV controlled substance classification.

Sponsored by:

Jurox Pty. Ltd.

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I. GENERAL INFORMATION:

A. File Number

NADA 141-342

B. Sponsor

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

Drug Labeler Code: 049480

U.S. Agent
James H. Schafer, D.V.M.
Schafer Veterinary Consultants, LLC
800 Helena Court
Fort Collins, CO 80524

C. Proprietary Name

ALFAXAN

D. Established Name

Alfaxalone

E. DEA Schedule

ALFAXAN (alfaxalone) is a substance with central nervous system (CNS) depressant properties, is a neurosteroid anesthetic that acts as an agonist at the gamma aminobutyric acid (GABA) receptor channel complex and is a Class IV controlled substance.

F. Pharmacological Category

Anesthetic

G. Dosage form

Injectable

H. Amount of Active Ingredients

10 mg/mL

I. How Supplied

10 mL single use vials

J. How Dispensed

Rx

K. Dosages

See below

L. Routes of Administration

Intravenous

M. Species/Classes

Cats and Dogs

N. 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.

O. Effect of Supplement

The supplement provides for the approval of the revised labeling components to reflect the placement of alfaxalone into Schedule IV controlled substance classification.

K. Dosages:

CAT DOSAGE

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

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

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

Table 1: ALFAXAN Induction Dose Guidelines: CATS

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

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

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

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

Table 2: ALFAXAN Maintenance Dose Guidelines: CATS

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

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

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

DOG DOSAGE

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

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

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

Table 3: ALFAXAN Induction Dose Guidelines: DOGS

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

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

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

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

Table 4: ALFAXAN Maintenance Dose Guidelines: DOGS

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

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

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

II. EFFECTIVENESS: CATS

A. Dosage Characterization

This supplemental approval does not change the previously approved dose guidelines 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 Freedom of Information (FOI) Summary for the original approval of NADA 141-342 dated September 6, 2012, contains dosage characterization information for species, dosage, or other applicable information.

B. Substantial Evidence of Effectiveness

CVM did not require effectiveness studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-342 dated September 6, 2012, contains a summary of studies that demonstrate effectiveness of the drug for species, dosage, or other applicable information.

III. EFFECTIVENESS: DOGS

A. Dosage Characterization

This supplemental approval does not change the previously approved dose guidelines 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 Freedom of Information (FOI) Summary for the original approval of NADA 141-342 dated September 6, 2012, contains dosage characterization information for species, dosage, or other applicable information.

B. Substantial Evidence of Effectiveness

CVM did not require effectiveness studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-342 dated September 6, 2014,

contains a summary of studies that demonstrate effectiveness of the drug for species, dosage, or other applicable information.

IV. TARGET ANIMAL SAFETY: CATS

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-342 dated September 6, 2012, contains a summary of target animal safety studies for species, dosage, or other applicable information.

V. TARGET ANIMAL SAFETY: DOGS

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-342 dated September 6, 2012, contains a summary of target animal safety studies for species, dosage, or other applicable information.

IV. HUMAN FOOD SAFETY

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

V. USER SAFETY

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

HUMAN WARNINGS: Not for human use. Keep out of the reach of children.

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

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

The Material Safety Data Sheet (MSDS) contains more detailed occupational safety information. To report adverse reactions in users or to obtain a copy of the MSDS for this product call 1-800-XXX-XXXX.

Note to physician: This product contains an injectable anesthetic.

DRUG ABUSE AND DEPENDENCE:
Controlled Substance: ALFAXAN contains alfaxalone, a neurosteroid anesthetic and 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 asses 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 with 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-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 and 21 CFR part 514. The data demonstrate that ALFAXAN, when used according to the label, is safe and effective for the induction and maintenance of anesthesia and for induction of anesthesia followed by maintenance with an inhalant anesthetic, in cats and dogs.

A. Marketing Status

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

B. Exclusivity

ALFAXAN, as approved in our approval letter, does not qualify for marketing exclusivity under section 512(c)(2)(F) of the Federal Food, Drug, and Cosmetic Act.

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.