

Date of Index Listing: January 22, 2020

FREEDOM OF INFORMATION SUMMARY

ORIGINAL REQUEST FOR ADDITION TO THE INDEX OF LEGALLY MARKETED
UNAPPROVED NEW ANIMAL DRUGS FOR MINOR SPECIES

MIF 900-031

Alfaxan® Multidose IDX
(alfaxalone)
Injectable Solution

For sedation and anesthesia in captive reptiles, excluding any food-producing species

For sedation and anesthesia in captive amphibians, excluding any food-producing species

For sedation and anesthesia in ornamental fish, including species used in research such as the zebra fish

For sedation and anesthesia in captive species and pet birds in the orders Psittaciformes, Passeriformes, and Columbiformes, excluding any food-producing species

For sedation and anesthesia in non-human primates

For sedation and anesthesia in captive rodents

For sedation and anesthesia in captive mustelids

For sedation and anesthesia in captive marsupials

For induction of anesthesia and immobilization in captive minor species ungulates, excluding any food-producing species

Requested by:
Jurox PTY LTD

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I. GENERAL INFORMATION:

File Number:

MIF 900-031

Requestor:

Jurox PTY LTD
85 Gardiner Street
Rutherford, New South Wales, 2320
Australia

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

Proprietary Name:

Alfaxalone

Established Name:

Alfaxan[®] Multidose IDX

Pharmacological Category:

Anesthetic; Drug Enforcement Agency (DEA) Schedule IV (CIV) controlled substance

Dosage Form:

Injectable solution

Amount of Active Ingredient:

10 mg alfaxalone/mL

How Supplied:

10 and 20 mL vials

How Dispensed:

by Prescription (Rx)

Dosage:

Dependent on species

Routes of Administration:

Intravascular (IV) injection, Intramuscular (IM) injection, Subcutaneous (SC) injection, Intraperitoneal (IP) injection, or Immersion

Species/Class:

Captive reptiles, captive amphibians, ornamental fish, captive species and pet birds in the orders Psittaciformes, Passeriformes, and Columbiformes, non-human

primates, captive rodents, captive mustelids, captive marsupials, captive minor species ungulates

Indications:

- For sedation and anesthesia in captive reptiles, excluding any food-producing species
- For sedation and anesthesia in captive amphibians, excluding any food-producing species
- For sedation and anesthesia in ornamental fish, including species used in research such as the zebra fish
- For sedation and anesthesia in captive species and pet birds in the orders Psittaciformes, Passeriformes, and Columbiformes, excluding any food-producing species
- For sedation and anesthesia in non-human primates
- For sedation and anesthesia in captive rodents
- For sedation and anesthesia in captive mustelids
- For sedation and anesthesia in captive marsupials
- For induction of anesthesia and immobilization in captive minor species ungulates, excluding any food-producing species

II. EFFECTIVENESS AND TARGET ANIMAL SAFETY:

In accordance with 21 CFR part 516, a qualified expert panel evaluated the target animal safety and effectiveness of Alfaxan® Multidose IDX, for sedation and anesthesia in multiple minor species, to determine whether the benefits of using Alfaxan® Multidose IDX for the proposed uses outweigh its risks to the target animals. The members of the qualified expert panel were:

Angela Lennox, DVM, DABVP (Avian), DECZM (Small Mammal) - Panel Leader

Nigel Caulkett, DVM, MVetSc, DACVAA

Cora Lau, PhD

Gregory Lewbart, MS, VMD, DACZM, DECZM (Zoo Health Management)

A. Findings of the Qualified Expert Panel:

The qualified expert panel thoroughly reviewed all available literature concerning the use of alfaxalone in the relevant minor species. Approximately one hundred and eight (108) articles were available for the review. Expert panel members conducted an in-depth review of each piece of literature and determined if the study design would allow conclusions on safety and effectiveness to be confidently relied upon. Results of the in-depth reviews were summarized, and conclusions were drawn regarding dose rates which could be confidently predicted to be safe and effective in the various minor species. Of the 108 articles reviewed by the expert panel, only information from 68 articles was

found acceptable for use in the construct of the dosage and administration section of the product labeling and package insert. The literature reviewed by the expert panel included the following species:

Amphibians	oriental fire-bellied toad, Australian frog, axolotl
Minor Species Birds	flamingo, swan, budgerigar, Bengalese finch
Ornamental Fish	goldfish, oscar, koi carp, zebrafish
Marsupials	koala, possum, glider, wombat, wallaby, kangaroo
Mustelids	ferret
Non-human primates	macaque, marmoset, lemur
Reptiles	red-bellied black snake, lowland copperhead snake, eastern tiger snake, coastal carpet python, black-headed python, ball python, garter snake, eastern bluetongue lizard, blotched bluetongue lizard, coastal bearded dragon, inland bearded dragon, Gippsland water dragon, green iguana, veiled chameleon, leopard gecko, perentie monitor, red-eared slider turtle, Hamann's tortoise, spur-thighed tortoise, marginated tortoise, Russian tortoise, Horsfield's tortoise, red-footed tortoise, pond slider, loggerhead sea turtle
Rodents	mice, rat, guinea pig, chinchilla
Minor Species Ungulates	alpaca

In addition, the expert panel members had varying degrees of personal experience with the use of alfaxalone for sedation and anesthesia of the minor species animals. Based on a thorough review of the literature, and their own personal experience, the qualified expert panel concluded that the benefits of using Alfaxan® Multidose IDX for sedation and anesthesia in captive reptiles, captive amphibians, ornamental fish, captive species and pet birds in the orders Psittaciformes, Passeriformes, and Columbiformes, non-human primates, captive rodents, captive mustelids, captive marsupials; and for induction of anesthesia and immobilization in minor species ungulates outweigh the risks to the target animals.

B. Literature Considered by the Qualified Expert Panel:

1. Adami C, d'Ovidio D, Casoni D. Alfaxalone-butorphanol versus alfaxalone-morphine combination for immersion anaesthesia in oriental fire-bellied toads (*Bombina orientalis*). *Lab Anim.* 2016 Jun; 50(3):204-11.
2. Ansel TV, Nour AK, Benavente-Perez A. The effect of anesthesia on blood pressure measured noninvasively by using the tail-cuff method in marmosets (*Callithrix jacchus*). *J Am Assoc Lab Anim Sci.* 2016; 55(5):594-600.
3. Arenillas M, Gomez de Segura IA. Anaesthetic effects of alfaxalone administered intraperitoneally alone or combined with dexmedetomidine and fentanyl in the rat. *Lab Anim.* 2018 Jan 0(0) 1-11.
4. Bakker J, Uilenreef JJ, Pelt ER, Brok HP, Remarque EJ, Langermans JA. Comparison of three different sedative-anaesthetic protocols (ketamine, ketamine-medetomidine and alphaxalone) in common marmosets (*Callithrix jacchus*). *BMC Vet Res.* 2013 Jun 11; 9:113.
5. Baldrey V. Assessment of Alfaxalone as an anaesthetic induction agent in mute swans (*Cygnus olor*) Submitted in part fulfilment of the requirements for the Royal College of Veterinary Surgeons' Diploma in Zoological Medicine 2014: 1-68.
6. Balko J, Lindemann D, Chinnadurai S. Evaluation of the anesthetic and cardiorespiratory effects of intramuscular alfaxalone compared with isoflurane inhalant and manual restraint in the budgerigar (*Melopsittacus undulates*). *Veterinary Anaesthesia and Analgesia.* 2017; 44:1262.e1e1262.e18.
7. Bauquier SH, Greenwood J, Whitem, T. Evaluation of the sedative and anaesthetic effects of five different concentrations of alfaxalone in goldfish, *Carassius auratus*. *Aquaculture.* 2013; 396-399:119-123.
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11. Bugman AM, Langer PT, Hadzima E, Rivas AE, Mitchell MA. Evaluation of the anesthetic efficacy of alfaxalone in oscar fish (*Astronotus ocellatus*). *Am J Vet Res.* 2016 Mar; 77(3):239-44.
12. Casoni D, Amen EM, Brecheisen M, Kuennecke B, Müggler T, Bergadano A. A combination of alfaxalone and medetomidine followed by an alfaxalone continuous rate infusion in cynomolgus monkeys (*Macaca fascicularis*) undergoing pharmacMRS. *Vet Anaesth Analg.* 2015 Sep; 42(5):552-4.
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14. del Álamo AM, Mandsager RE, Riebold TW, Payton ME. Evaluation of intravenous administration of alfaxalone, propofol, and ketamine-diazepam for anesthesia in alpacas. *Vet Anaesth Analg*. 2015 Jan; 42(1): 72-82.
15. Doerning CM, Bradley MP, Lester PA, Nowland MH. Effects of subcutaneous alfaxalone alone and in combination with dexmedetomidine and buprenorphine in guinea pigs (*Cavia porcellus*). *Vet Anaesth Analg*. 2018 Sep; 45(5): 658-666.
16. Doss GA, Fink DM, Sladky KK, Mans C. Comparison of subcutaneous dexmedetomidine-midazolam versus alfaxalone-midazolam sedation in leopard geckos (*Eublepharis macularius*). *Vet Anaesth Analg*. 2017 Sep; 44(5): 1175-1183.
17. d'Ovidio D, Marino F, Noviello E, Lanaro E, Monticelli P, Adami C. Sedative effects of intramuscular alfaxalone in pet guinea pigs (*Cavia porcellus*). *Vet Anaesth Analg*. 2018 Mar; 45(2): 183-189.
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21. Goodwin WA and Pasloske K. A dose ranging study evaluating the pharmacodynamics of RD0327 as an anaesthetic and sedative in rabbits after Intramuscular injection. Oral abstract (O14-1, pg. 161). Presented at the World Congress of Veterinary Anesthesiology, September 2nd, 2015, Kyoto, Japan.
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27. James LE, Williams CJ, Bertelsen MF, Wang T. Anaesthetic induction with alfaxalone in the ball python (*Python regius*): dose response and effect of injection site. *Vet Anaesth Analg*. 2018 May;45(3):329-337.
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33. Liddle V, Naranjo C, Bernays M. Anterior chamber collapse syndrome in a koala. *Aust Vet J*. 2014 May;92(5):179-82.
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46. Perrin KL, Bertelsen MF. Intravenous alfaxalone and propofol anesthesia in the bearded dragon (*Pogona vitticeps*). *Herpetol. Med. Surg.* 2017; 27(3-4): 123-126.
47. Perrin KL, Nielsen JB, Thomsen AF, Bertelsen MF. Alfaxalone anesthesia in the bengalese finch (*Lonchura domestica*). *J Zoo Wildl Med.* 2017 Dec; 48(4): 1146-1153.
48. Phillips BE, Posner LP, Lewbart GA, Christiansen EF, Harms CA. Effects of alfaxalone administered intravenously to healthy yearling loggerhead sea turtles (*Caretta caretta*) at three different doses. *J Am Vet Med Assoc.* 2017 Apr 15; 250(8): 909-917.
49. Pypendop BH, Ranasinghe MG, Pasloske K. Comparison of two intravenous anesthetic infusion regimens for alfaxalone in cats. *Vet Anaesth Analg* 2018. Jul 45(4): 459-466.
50. Pypendop BH, Ranasinghe MG, Pasloske K. Pharmacokinetics of alfaxalone infusions, context-sensitive half time and recovery times in male neutered cats. *Vet Anaesth Analg* 2018; Sep (45(5): 630-639.
51. Pypendop BH, Siao KT, Ranasinghe MG, Pasloske K. Effective plasma alfaxalone concentration to produce immobility in male neutered cats. *Vet Anaesth Analg* 2018. May 45(3); 269-277.
52. Radkey DI, Hardie RJ, Smith LJ. Comparison of the effects of alfaxalone and propofol with acepromazine, butorphanol and/or doxapram on laryngeal motion and quality of examination in dogs. *Vet Anaesth Analg* 2018; May 45(3): 241-249.
53. Reynolds PS, Song KS, Tamariz FJ, Wayne Barbee R. Hypertension and vulnerability to hemorrhagic shock in a rat model. *Shock.* 2015 Feb; 43(2): 148-56.
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59. Sladakovic I, Johnson RS, Vogelnest L. Evaluation of intramuscular alfaxalone in three Australian frog species (*Litoria caerulea*, *Litoria aurea*, *Litoria booroolongensis*). *J. Herpetol. Med. Surg.* 2014;24(1–2):36-42.
60. Strahl-Heldreth D, Clark-Price S, Keating S, Graham L, Chinnadurai S. The effect of intracoelomic alfaxalone on righting reflex and response to Semmes-Weinstein monofilaments in the common garter snake (*Thamnophis sirtalis*). *Veterinary Anaesthesia and Analgesia.* 44, 1262.e1e1262.e18.
61. Thas I. Acquired salivary mucoceles in two domestic ferrets (*Mustela putorius furo*). *Vet Rec Case Rep* 2014 2: 1-8.
62. Thomas AA, Leach MC, Flecknell PA. An alternative method of endotracheal intubation of common marmosets (*Callithrix jacchus*). *Lab Anim.* 2012 Jan;46(1):71-6.
63. Tremoleda JL, Kerton A, Gsell W. Anaesthesia and physiological monitoring during in vivo imaging of laboratory rodents: considerations on experimental outcomes and animal welfare. *EJNMMI Res.* 2012 Aug 9;2(1):44.
64. Tribe A, Hanger J, McDonald IJ, Loader J, Nottidge BJ, McKee JJ, Phillips CJ. A reproductive management program for an urban population of eastern grey kangaroos (*Macropus giganteus*). *Animals (Basel).* 2014 Sep 15;4(3):562-82.
65. Villaverde-Morcillo S, Benito J, García-Sánchez R, Martín-Jurado O, Gómez de Segura IA. Comparison of isoflurane and alfaxalone (Alfaxan) for the induction of anesthesia in flamingos (*Phoenicopterus roseus*) undergoing orthopedic surgery. *J Zoo Wildl Med.* 2014 Jun;45(2):361-6.
66. Vogelnest L. Marsupialia (Marsupials). *Fowler's Zoo and Wild Animal Medicine.* 2014; Volume 8, Chapter 33, p.260.
67. Waugh C, Khan SA, Carver S, Hanger J, Loader J, Polkinghorne A, Beagley K, Timms P. A prototype recombinant-protein based *Chlamydia pecorum* vaccine results in reduced chlamydial burden and less clinical disease in free-ranging koalas (*Phascolarctos cinereus*). *PLoS One.* 2016 Jan 12;11(1):1-9.
68. White KL, Paine S, Harris J. A clinical evaluation of the pharmacokinetics and pharmacodynamics of intravenous alfaxalone in cyclodextrin in male and female rats following a loading dose and constant rate infusion. *Vet Anaesth Analg.* 2017 Jul;44(4):865-875.

III. USER SAFETY:

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

WARNINGS

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

Alfaxan[®] Multidose IDX 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 1-844-253-2926.

Note to physician: This product contains an injectable anesthetic.

DRUG ABUSE AND DEPENDENCE

Controlled substance: Alfaxan[®] Multidose IDX 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 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.

IV. AGENCY CONCLUSIONS:

The information submitted in support of this request for Alfaxan[®] Multidose IDX for addition to the Index of Legally Marketed Unapproved New Animal Drugs for Minor Species (Index) for the following intended uses satisfies the requirements of section 572 of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 516:

- For sedation and anesthesia in captive reptiles, excluding any food-producing species
- For sedation and anesthesia in captive amphibians, excluding any food-producing species
- For sedation and anesthesia in ornamental fish, including species used in research such as the zebra fish
- For sedation and anesthesia in captive species and pet birds in the orders Psittaciformes, Passeriformes, and Columbiformes, excluding any food-producing species
- For sedation and anesthesia in non-human primates
- For sedation and anesthesia in captive rodents
- For sedation and anesthesia in captive mustelids
- For sedation and anesthesia in captive marsupials
- For induction of anesthesia and immobilization in captive minor species ungulates, excluding any food-producing species

A. Determination of Eligibility for Indexing:

As part of the determination of eligibility for inclusion in the Index, FDA determined that the drug for this intended use was safe to the user, did not individually or cumulatively have a significant effect on the human environment, and that the description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the new animal drug was sufficient to demonstrate that the requestor has established appropriate specifications for the manufacture of the new animal drug. Additionally, the requestor has committed to manufacture the drug in accordance with current good manufacturing practices (cGMP).

The Index is only available for new animal drugs intended for use in minor species for which there is a reasonable certainty that the animal or edible products from the animal will not be consumed by humans or food-producing animals and for new animal drugs intended for use only in a hatchery, tank, pond, or other similar contained man-made structure in an early, non-food life stage of a food-producing minor species, where safety for humans is demonstrated in accordance with the standard of section 512(d) of the act. Because this new animal drug is not intended for use in food-producing animals, FDA did not require data pertaining to drug residues in food (i.e., human food safety) for granting this request for addition to the Index.

B. Qualified Expert Panel:

The qualified expert panel for Alfaxan® Multidose IDX met the selection criteria listed in 21 CFR 516.141(b). The panel satisfactorily completed its responsibilities in accordance with 21 CFR part 516 in determining the target animal safety and effectiveness of Alfaxan® Multidose IDX for sedation and anesthesia in captive

reptiles, captive amphibians, ornamental fish, captive species and pet birds in the orders Psittaciformes, Passeriformes, and Columbiformes, non-human primates, captive rodents, captive mustelids, captive marsupials; and for induction of anesthesia and immobilization in minor species ungulates.

C. Marketing Status:

Alfaxan[®] Multidose IDX will be marketed by prescription.

D. Exclusivity:

Products listed in the Index do not qualify for exclusive marketing rights.