

# Alfaxan® Multidose FAQ



## 1. Is there a difference between Alfaxan® Multidose and Alfaxan® Multidose IDX?

[Alfaxan® Multidose IDX](#) is an [indexed product](#), meaning it went through a different product approval process than [Alfaxan® Multidose](#) for cats and dogs (click links to access the prescribing information and details on indexing). Indexed products are registered through the Minor Use Minor Species (MUMS) Office of the FDA. Major species product approvals (e.g., cat and dog) are registered through the Office of New Animal Drug Evaluation (ONADE) of the FDA, Center for Veterinary Medicine. Indexing allows products indicated for species that are too varied or rare to complete the traditional safety studies to go through an alternate review process. Therefore, Alfaxan® Multidose IDX and Alfaxan® Multidose are two distinct products with different label indications. However, the products Alfaxan® Multidose and Alfaxan® Multidose IDX are chemically identical. While the two products are chemically identical, specific product indications are that Alfaxan® Multidose is approved for dogs and cats and Alfaxan® Multidose IDX is approved for more than 50, non-food-producing minor species.

## 2. Can Alfaxan® Multidose be administered to dogs for cesarean sections?

The safety and efficacy of alfaxalone anesthetic induction, followed by anesthetic maintenance with isoflurane in oxygen, in bitches and their litters have been reported in multiple published studies in dogs undergoing both elective and emergency cesarean section. In all of these studies, neonatal vigor scores (i.e. modified APGAR [appearance, pulse, grimace, activity respiration] scores) were good or very good. The reported anesthetic stability and rapid neonatal resuscitation in these studies are consistent with alfaxalone's short duration of action, rapid clearance, and minimal cardiorespiratory depression. Current scientific evidence supports the use of alfaxalone as an induction agent for cesarean sections and suggests that maintenance with inhalant anesthetics or a combination of inhalant and intravenous techniques may achieve the best results. For further information on this topic, see the [General Anesthesia for Cesarean Section in Dogs and Cats](#) article and [Pregnancy, C-sections, and Pediatrics](#) webinar on our [Think Anesthesia®](#) educational website.

*Doebeli A, Michel E, Bettschart R, Hartnack S, Reichler IM. Apgar score after induction of anesthesia for canine cesarean section with alfaxalone versus propofol. Theriogenology. 2013 Nov;80(8):850-4.*

*Metcalfe S, Hulands-Nave A, Bell M, Kidd C, Pasloske K, O'Hagan B, Perkins N, Whitem T. Multicentre, randomised clinical trial evaluating the efficacy and safety of alfaxalone administered to bitches for induction of anaesthesia prior to caesarean section. Aust Vet J. 2014 Sep;92(9):333-8.*

*Melandri M, Alonge S, Peric T, Bolis B, Veronesi MC. Effects of Alfaxalone or Propofol on Giant-Breed Dog Neonates Viability During Elective Caesarean Sections. Animals (Basel). 2019 Nov 13;9(11).*

*Conde Ruiz C, Del Carro AP, Rosset E, Guyot E, Maroiller L, Buff S, Portier K. Alfaxalone for total intravenous anaesthesia in bitches undergoing elective caesarean section and its effects on puppies: a randomized clinical trial. Vet Anaesth Analg. 2016 May;43(3):281-90.*

## 3. Can Alfaxan® Multidose be administered to dogs with the MDR1 gene mutation?

Alfaxalone was tested by Dr. Katrina Mealey's laboratory at Washington State University at 1-10 µg/mL (i.e. effective blood concentration) as a substrate for the P glycoprotein pump. Results showed that it is not a substrate for canine P-glycoprotein. This means that there should be no differences in the response to Alfaxan® Multidose in animals with the MDR1 mutation. One publication reporting the use of alfaxalone in a patient with confirmed MDR1 mutation was assessing the use of alfaxalone in dogs undergoing cesarean section. One border collie was confirmed to have the mutation and no issues arose. The Clinical Pharmacology Laboratory at Washington State University has some comprehensive information on this mutation, including a list of problem drugs which can be found at <http://vcpl.vetmed.wsu.edu/problem-drugs>.

*Conde Ruiz C, Del Carro AP, Rosset E, Guyot E, Maroiller L, Buff S, Portier K. Alfaxalone for total intravenous anaesthesia in bitches undergoing elective caesarean section and its effects on puppies: a randomized clinical trial. Vet Anaesth Analg. 2016 May;43(3):281-90.*



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#### 4. What effect does Alfaxan® Multidose have on laryngeal function?

Oral laryngoscopy is performed after administration of injectable anesthesia to evaluate laryngeal function in patients suspected of having laryngeal paralysis. The injectable anesthetic drug used should provide good jaw muscle relaxation to allow visualization of the rima glottis and sufficient inspiratory efforts by the patient must be present to be able to visualize and assess function of the cricoarytenoideus dorsalis muscle. The effect of alfaxalone on laryngeal function, with and without premedication, has been reported in dogs and cats to be similar to other injectable anesthetic drugs and, therefore, Alfaxan® Multidose can be used to properly evaluate laryngeal function in both dogs and cats.

*Radkey DJ, 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;45:241–249.*

*Nelissen P, Corletto F, Aprea F, et al. Effect of three anesthetic induction protocols on laryngeal motion during laryngoscopy in normal cats. Vet Surg 2012;41:876–883.*

*Norgate D, Ter Haar G, Kulendra N, et al. A comparison of the effect of propofol and alfaxalone on laryngeal motion in nonbrachycephalic and brachycephalic dogs. Vet Anaesth Analg 2018;45:729–736.*

*Ambros B, Gaunt MC, Duke-Novakovski T, et al. Effects of alfaxalone, thiopental, or propofol and diazepam on laryngeal motion in healthy dogs. Can Vet J 2018;59:791–795.*

*Smalle TM, Hartman MJ, Bester L, et al. Effects of thiopentone, propofol and alfaxalone on laryngeal motion during oral laryngoscopy in healthy dogs. Vet Anaesth Analg 2017;44:427–434.*

#### 5. What effect does Alfaxan® Multidose have on intraocular pressure in dogs?

Injectable anesthetic drugs can increase intraocular pressure, which can be deleterious in patients with glaucoma or corneal lesions. No significant difference in intraocular pressure has been reported in dogs between alfaxalone and propofol (Hasiuk 2013, Costa 2015). An insignificant increase in IOP has been reported two minutes after an IV bolus of alfaxalone, followed by a significant decrease in IOP for 25 minutes (Costa 2015). In both unpremedicated and premedicated healthy dogs, IOP increased following alfaxalone administration, with the highest IOP associated with intubation (Bauer 2016). While dogs premedicated and induced with alfaxalone had a significant increase in IOP, these values remained within the normal canine physiological range (Mayordomo-Febrer 2017). When anesthetizing patients with glaucoma or loss of globe integrity, it is also important to consider other factors that can increase IOP, including physical restraint, orotracheal intubation, positioning of the patient's head below the body, hypoxemia, and hypercapnia.

*Hasiuk MM, Forde N, Cooke A, Ramey K, Pang DS. A comparison of alfaxalone and propofol on intraocular pressure in healthy dogs. Vet Ophthalmol. 2014 Nov;17(6):411–6. doi: 10.1111/vop.12119. Epub 2013 Nov 18.*

*Costa D, Leiva M, Moll X, Aguilar A, Peña T, Andaluz A. Alfaxalone versus propofol in dogs: a randomised trial to assess effects on peri-induction tear production, intraocular pressure and globe position. Vet Rec. 2015 Jan 17;176(3):73. doi: 10.1136/vr.102621. Epub 2014 Oct 16.*

*Bauer BS, Ambros B. The effects of intravenous alfaxalone with and without premedication on intraocular pressure in healthy dogs. Can J Vet Res. 2016;80(2):156–161.*

*Mayordomo-Febrer A, Rubio M, Martínez-Gassent M, López-Murcia MM. Effects of morphine-alfaxalone-midazolam premedication, alfaxalone induction and sevoflurane maintenance on intraocular pressure and tear production in dogs. Vet Rec. 2017 May 13;180(19):474. doi: 10.1136/vr.104040. Epub 2017 Jan 6.*

#### 6. What effect does Alfaxan® Multidose have on echocardiographic measurements?

Echocardiography often needs to be performed with sedation and ideally, this sedation should not alter the measured variables. In cats administered 2 mg/kg alfaxalone with other medications (0.2 mg/kg butorphanol or 0.3 mg/kg methadone and 1 mg/kg ketamine) IM, sedation was adequate and there were not clinically meaningful effects on the measured echocardiographic variables (Ribas 2014, Lazzarini 2020). Cats administered 5 mg/kg alfaxalone IM were also appropriately sedated, however a decrease in aortic root diameter occurred (from 0.84 [0.69, 1.2] to 0.82 [0.62, 1.16] cm) with the remainder of echocardiographic variables unchanged (Kim 2019).

Dogs administered 3 mg/kg alfaxalone IV for echocardiography showed mild cardiovascular depression that was neither clinically nor statistically significant (Kim 2015). In dogs administered 4 mg/kg alfaxalone IM, mild changes in echocardiographic variables, heart rate, and mean arterial pressure were observed (Cruz-Benedetti 2018).

Lazzarini E, Martinelli E, Brioschi FA, et al. Intramuscular alfaxalone and methadone with or without ketamine in healthy cats: effects on sedation and echocardiographic measurements. *Vet Anaesth Analg* 2020;47:621–630.

Ribas T, Bublot I, Junot S, Beaufrère H, Rannou B, Gagnière P, Cadoré JL, Pariaut R. Effects of intramuscular sedation with alfaxalone and butorphanol on echocardiographic measurements in healthy cats. *J Feline Med Surg*. 2014 Jun;17(6):530-6.

Kim B, Jang M, Sohn J, et al. Effects of Intramuscular Alfaxalone/Acepromazine on Echocardiographic, Biochemical, and Blood Gas Measurements in Healthy Cats. *J Am Anim Hosp Assoc* 2019;55:70–77.

Kim Y-W, Kim T-J, Hyun C. Effects of alfaxalone on echocardiographic examination in healthy dogs. *Korean J Vet Res* 2015;55(4):221–225.

Cruz-Benedetti IC, Bublot I, Ribas T, Fourel I, Vogl C, Dubois C, Milani M, Ida KK, Portier K. Pharmacokinetics of intramuscular alfaxalone and its echocardiographic, cardiopulmonary and sedative effects in healthy dogs. *PLoS One*. 2018 Sep 24;13(9):e0204553.

## **7. Can Alfaxan® Multidose be administered to patients with hepatic disease?**

Many anesthetic and analgesic drugs used in veterinary medicine undergo hepatic metabolism, and a reduced rate of metabolism can result in a prolonged and a potentially unpredictable period of action (Tonge, 2021). The liver is the major metabolic organ for the inactivation of alfaxalone, with inactive alfaxalone metabolites cleared by the kidney (Warne 2015). Plasma protein binding for alfaxalone is 97% (Sewell 2004). Hypoalbuminemia, often a sequela to hepatic disease, can lead to a greater plasma concentration of unbound, active drug which can potentially delay recovery. Although there are no studies specifically evaluating alfaxalone in dogs or cats with liver disease, alfaxalone has been administered safely and effectively in human patients with hepatic cirrhosis (Strunin et al., 1977), veterinary patients undergoing portosystemic shunt surgery (Hunt 2004, Psatha 2011), and in a cat diagnosed with hepatic lipidosis and gallbladder mucocoele (Bennet 2007).

It is important to remember, when anesthetizing any systemically ill patient, it is best to administer the anesthetic induction drug slowly to effect, to provide the lowest dose necessary to achieve a surgical plane of anesthesia and endotracheal intubation. This concept of “titrate to effect” is even more critical when a patient is presented to the clinician with hepatic disease where metabolism may be delayed and or the patient requires less alfaxalone than that observed in the healthy population.

Bennett SL, Milne M, Slocombe RF, Landon BP. Gallbladder mucocoele and concurrent hepatic lipidosis in a cat. *Aust Vet J*. 2007 Oct;85(10):397-400

Hunt GB, Kummeling A, Tisdall PLC, et al. Outcomes of Cellophane Banding for Congenital Portosystemic Shunts in 106 Dogs and 5 Cats. *Vet Surg* 2004;33:25–31.

Psatha E, Alibhai HI, Jimenez-Lozano A, et al. Clinical efficacy and cardiorespiratory effects of alfaxalone, or diazepam/fentanyl for induction of anaesthesia in dogs that are a poor anaesthetic risk. *Vet Anaesth Analg* 2011;38(1):24–36.

Sewell JC, Sear JW. Derivation of preliminary three-dimensional pharmacophoric maps for chemically diverse intravenous general anaesthetics. *Br J Anaesth*. 2004 Jan;92(1):45-53.

Strunin L et al. Metabolism of 14C-Labelled alphaxalone in man. *Br J Anaesth* 1977;49:609-614

Tonge, Emily. (2021) Sedation and general anaesthesia of the portosystemic shunt patient. *Companion Animal*, Volume 26 Number 5: 1-9.

Warne, L. N., Beths, T., Whitem, T., et al. (2015) A review of the pharmacology and clinical application of alfaxalone in cats. *The Vet Journal*, 203: 141–148.

## **8. What effect does Alfaxan® Multidose have on intracranial pressure and other vascular brain parameters?**

During anesthesia in patients with increases in intracranial pressure (ICP), minimizing ICP while maintaining cerebral

perfusion pressure (CPP, the difference between mean arterial pressure (MAP) and ICP) are key to preventing ischemia and brain damage. Alfaxalone causes minimal cardiovascular effects and the patient's MAP is usually well maintained, which contributes to the maintenance of an acceptable CPP (Muir 2008, 2009). Alfaxalone causes a dose-dependent decrease in cerebral blood flow (CBF) while maintaining cerebrovascular reactivity to carbon dioxide (CVR-CO<sub>2</sub>) in dogs, both of which are desirable in patients with increased ICP. Similar changes have been observed with propofol anesthesia, although CBF was significantly lower, and CVR-CO<sub>2</sub> was higher during hypocapnia with alfaxalone compared to propofol. Conversely, in the same study, CBF increased, and CVR-CO<sub>2</sub> was decreased in dogs induced and maintained on isoflurane (Bini 2020). In cats administered a previously registered Cremophor®-EL-based formulation of alfaxalone and alfadolone (another neurosteroid), similar changes were reported, with decreased cerebral blood flow (CBF), ICP, and maintenance of CVR-CO<sub>2</sub> responsiveness, although at a deeper plane of anesthesia autoregulation of CBF was transiently abolished (Baldy-Moulinier 1975). Alfaxalone administered as a single anesthetic drug for functional magnetic resonance imaging (fMRI) in cats provided more stable respiratory rates and evoked a more consistent blood-oxygen-level-dependent (BOLD) signal across animals compared to ketamine and isoflurane (Levine 2020). Alfaxalone, in combination with remifentanyl, has been successfully administered for total intravenous anesthesia in a dog undergoing a craniectomy and temporal lobectomy (Warne 2014).

Baldy-Moulinier M, Besset-Lehmann J, Passouant P. [Effects of combination alfaxalone and alfadolone, anesthetic derivatives of pregnanedione, on cerebral hemodynamics in cats]. *C R Seances Soc Biol Fil* 1975;169:126–131.

Bini G, Bailey K, Voyvodic J, et al. Effects of propofol, alfaxalone and isoflurane on cerebral blood flow and cerebrovascular reactivity to CO<sub>2</sub> in dogs. *Vet Anaesth Analg* 2020;47:855e2 (abstract only).

Levine AT, Li B, Barnes P, et al. Assessment of anesthesia on physiological stability and BOLD signal reliability during visual or acoustic stimulation in the cat. *J Neurosci Methods* 2020;334:108603 (online ahead of print).

Muir W, Lerche P, Wiese A, et al. Cardiorespiratory and anesthetic effects of clinical and supraclinical doses of alfaxalone in dogs. *Vet Anaesth Analg* 2008;35:451–462.

Muir W, Lerche P, Wiese A, et al. The cardiorespiratory and anesthetic effects of clinical and supraclinical doses of alfaxalone in cats. *Vet Anaesth Analg* 2009;36:42–54.

Warne LN, Beths T, Fogal S, Bauquier SH. The use of alfaxalone and remifentanyl total intravenous anesthesia in a dog undergoing a craniectomy for tumor resection. *Can Vet J* 2014 Nov;55(11):1083–1088.

## 8. What effects do injectable and inhalant anesthetic drugs have on the renal system?

For patients with renal disease or patients that may be predisposed to acute renal injury (AKI) following an anesthetic procedure, the anesthetist's priorities should include maintenance of normotension, establishing and maintaining euvoolemia and an effort to maintain renal blood perfusion through optimization of cardiac output. These three cardiovascular objectives influence the choice of anesthetic drugs administered to the patient and how to best stabilize the patient's fluid status and blood pressure prior to the procedure in order to minimize the occurrence of AKI during or following the anesthetic event. Anesthetic drugs have, therefore, been studied to determine what effect they have on the kidney and its functions. Most of these studies have been in the healthy patient. The injectable GABAergic anesthetic drugs, including propofol, etomidate and thiopental, in combination with isoflurane maintenance have been investigated in healthy purpose-bred dogs. There was no statistically significant differences in GFR among the treatment groups. The authors concluded that any of these injectable anesthetics could be administered for anesthetic induction followed by isoflurane maintenance without adversely affecting GFR in healthy dogs (Chang 2011). Ketamine is metabolized by most species via the liver and can be administered in dogs with renal disease. Cats, however, are unable to completely metabolize ketamine and the active metabolite norketamine is heavily dependent on renal excretion. It is, therefore, recommended in moderate to severe renal disease in cats, ketamine be avoided, when possible, to avoid prolonged effects (Rezende 2015, Hannah 1988).

In summary, GABAergic injectable anesthetic drugs, including alfaxalone, are preferred in patients with renal disease or patients prone to AKI. When dogs or cats with renal disease are being anesthetized, the anesthetist should take measures to understand the patient's fluid and blood pressure status before induction and repeatedly monitor these parameters throughout the peri-anesthetic period.

Chang, J et al. Evaluation of the effects of thiopental, propofol, and etomidate on glomerular filtration rate measured by the use of dynamic



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*computed tomography in dogs. Am J Vet Res. 2011 Jan;72(1):146-51.*

*Rezende M & Khursheed M. Anesthesia for patients with renal disease. Clinician's Brief. 2015;41-44.*

*Hanna RM, Borchard RE, Schmidt SL. 1988. Pharmacokinetics of ketamine HCl and metabolite I in the cat: a comparison of IV, IM, and rectal administration. J Vet Pharmacol Ther. 1988 Mar;11(1):84-93.*



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