SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Alfaxan 10 mg/ml solution for injection for dogs, cats and pet rabbits

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
alfaxalone 10 mg/ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection
Clear colourless solution

4. CLINICAL PARTICULARS

4.1 Target species

Dogs, cats and non-food rabbits

4.2 Indications for use, specifying the target species

As an induction agent prior to inhalation anaesthesia in cats, dogs and non-food rabbits.

As a sole anaesthetic agent for the induction and maintenance of anaesthesia for the performance of examination or surgical procedures in cats and dogs.

4.3 Contraindications

Do not use in combination with other intravenous anaesthetic agents.

4.4 Special warnings

During recovery, it is preferable that animals are not handled or disturbed. In dogs and cats, this may lead to paddling, minor muscle twitching or movements that are more violent. While better avoided, such reactions are clinically insignificant.

4.5 Special precautions for use

(i) Special precautions for use in animals

The analgesic properties of alfaxalone are limited, therefore appropriate peri-operative analgesia should be provided in cases where procedures are anticipated to be painful.

The safety of the veterinary medicinal product in animals less than 12 weeks of age (dogs and cats) and 16 weeks of age (rabbits) has not been demonstrated.

Transient post induction apnoea frequently occurs, particularly in dogs – see section 4.6 for details. In such cases, endotracheal intubation and oxygen supplementation should be employed. Facilities for intermittent positive pressure ventilation should be available. In order to minimise the possibility of apnoea, administer the veterinary medicinal product by slow intravenous injection and not as a rapid dose.

Especially when using higher doses of the veterinary medicinal product, a dose-dependent respiratory depression may occur. Oxygen and/or intermittent positive pressure ventilation should be administered to counteract the threatening hypoxaemia/hypercapnea. This should be particularly important in risky anaesthetic cases and whenever the anaesthesia is to be carried out for a longer period of time. In rabbits, oxygenation is essential before induction of anaesthesia and throughout the entire anaesthetic procedure to avoid potentially life-threatening hypoxaemia.

In dogs and cats, the dose interval for maintenance of anaesthesia by intermittent bolus administration may require lengthening by more than 20%, or the maintenance dose by intravenous infusion may require reduction by more than 20%, when hepatic blood flow is severely diminished or hepatocellular injury is severe. In cats or dogs with renal insufficiency, doses for induction and maintenance may require reduction.

As with all general anaesthetic agents:

- It is advisable to ensure that dogs and cats have been fasted before receiving the anaesthetic. Rabbits should not be fasted, but food should be removed one hour before anaesthesia
- As with other intravenous anaesthetic agents, caution should be exercised in animals with cardiac or respiratory impairment, or in hypovolaemic or debilitated animals.
- Additional monitoring is advised and particular attention should be paid to respiratory parameters in aged animals, or in cases where there may be additional physiological stress imposed by pre-existing pathology, shock or caesarean section.
- Following induction of anaesthesia, the use of an endotracheal tube is recommended to maintain airway patency.
- It is advisable to administer supplemental oxygen during maintenance of anaesthesia.

- Respiratory embarrassment may occur – ventilation of the lungs with oxygen should be considered if haemoglobin saturation with oxygen (SpO_2%) falls below 90% or if apnoea persists for longer than 60 seconds.
- If cardiac arrhythmias are detected, attention to respiratory ventilation with oxygen is the first priority followed by appropriate cardiac therapy or intervention.

Psychomotor excitement may be encountered in a minority of dogs and cats recovering from anaesthesia with the veterinary medicinal product. Post-anaesthetic recovery should thus take place in appropriate facilities and under sufficient supervision. Use of a benzodiazepine as the sole premedicant in dogs and cats may increase the probability of psychomotor excitement.

Muscle twitching/tremors may be observed in a small proportion of rabbits anaesthetised with Alfaxan; however, such reactions are not considered to be clinically significant.

(ii) Special precautions to be taken by the person administering the veterinary medicinal product to animals

This product is a sedative, exercise caution to avoid accidental self-injection. Preferably use a guarded needle until the moment of injection.
In case of accidental self-injection seek immediate medical attention and show the product literature.
The product may cause irritation if it comes into contact with the skin or eyes. Rinse any splashes from skin or eyes immediately with water.

4.6 Adverse reactions (frequency and seriousness)

In clinical studies using the veterinary medicinal product, 44% of dogs, 19% of cats and 7% of rabbits experienced post induction apnoea, which was defined as the cessation of breathing for 30 seconds or more. The mean duration of apnoea in these animals was 100 seconds in dogs, 60 seconds in cats and 53 seconds in rabbits. Endotracheal intubation and oxygen supplementation should therefore be employed. In rabbits, oxygenation prior to administration of the product for induction of anaesthesia is essential in order to reduce the risk of life-threatening hypoxaemia post-induction occurring secondary to respiratory depression or apnoea.

In rabbits, behavioural reactions such as head-shaking may be observed during intravenous (marginal ear vein) administration, therefore a pre-placed IV catheter is recommended.

Based on post marketing safety experience, neurological signs (convulsions, myoclonus, tremor, prolonged anaesthesia), cardio-respiratory signs (cardiac arrests, bradycardia, bradypnea) and behavioural signs (hyperactivity, vocalisation) have been reported very rarely.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))

- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

4.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established in cases where pregnancy is to be continued or during lactation. Its effects upon fertility have not been evaluated. However, studies using alfaxalone in pregnant mice, rats and rabbits have demonstrated no deleterious effects on gestation of the treated animals, or on the reproductive performance of their offspring. The product should be used in pregnant animals according to the risk-benefit assessment performed by the veterinarian. The product has been safely used in dogs for the induction of anaesthesia prior to delivery of puppies by caesarean section. In these studies, dogs were not premedicated, a dose of 1-2 mg/kg was drawn up (i.e. slightly lower than the usual 3 mg/kg dose, see section 4.9) and the product was administered as recommended, to effect.

4.8 Interaction with other medicinal products and other forms of interaction

In dogs and cats, the veterinary medicinal product has been demonstrated to be safe when used in combination with the following premedicant classes:

Drug Class	**Examples**
Phenothiazines	acepromazine maleate
Anticholinergic agents	atropine sulfate
Benzodiazepines	diazepam, midazolam hydrochloride,
Alpha-2-adrenoceptor agonists	xylazine hydrochloride, medetomidine hydrochloride
Opiates	methadone, morphine sulfate, butorphanol tartrate, buprenorphine hydrochloride
NSAIDs	carprofen, meloxicam

During clinical studies in rabbits, the veterinary medicinal product was used safely with the following premedicant combinations: (i) medetomidine hydrochloride in combination with buprenorphine hydrochloride or butorphanol tartrate, and (ii) midazolam hydrochloride in combination with buprenorphine hydrochloride or butorphanol tartrate.

The concomitant use of other CNS depressants should be expected to potentiate the depressant effects of the veterinary medicinal product, necessitating cessation of further administration of the veterinary medicinal product when the required depth of anaesthesia has been reached.

The use of one premedicant or a combination of premedicants often reduces the dose of the veterinary medicinal product required.

Premedication with alpha-2-adrenoceptor agonists such as xylazine and medetomidine can markedly increase the duration of anaesthesia in a dose dependent fashion. In order to shorten recovery periods it may be desirable to reverse the actions of these premedicants.

Benzodiazepines should not be used as sole premedicants in dogs and cats as the quality of anaesthesia in some patients may be sub-optimal. Benzodiazepines may be used safely and effectively in combination with other premedicants and the veterinary medicinal product.

Refer to section 4.3.

4.9 Amounts to be administered and administration route

For intravenous use

Induction of anaesthesia:
The induction dose of the veterinary medicinal product is based on data taken from controlled laboratory and field studies and is the amount of drug required for 9 of 10 patients (i.e. 90th percentile) to be successfully induced for anaesthesia.

Dosing recommendations for induction of anaesthesia are as follows:

	DOGS		CATS		RABBITS	
	Un-premedicated	Premedicated	Un-premedicated	Premedicated	Un-premedicated	Premedicated
mg/kg	3	2	5	5	5	4
ml/kg	0.3	0.2	0.5	0.5	0.5	0.4

The dosing syringe should be prepared to contain the above dose. Administration should continue until the clinician is satisfied that the depth of anaesthesia is sufficient for endotracheal intubation, or until the entire dose has been administered. The necessary injection rate can be achieved by administration of one quarter (¼) of the calculated dose every 15 seconds, so that the total dose, if required, would be administered over the first 60 seconds. If, 60 seconds after complete delivery of this first induction dose, intubation is still not possible, one further similar dose may be administered to effect.

Maintenance of anaesthesia:
Following induction of anaesthesia with the veterinary medicinal product, the animal may be intubated and maintained on the veterinary medicinal product or an inhalation anaesthetic agent.

In dogs and cats maintenance doses of the veterinary medicinal product may be given as supplemental boluses or as constant rate infusion. The veterinary medicinal product has been used safely and effectively in dogs and cats for procedures lasting for up to one hour. The following doses suggested for maintenance of anaesthesia are based on data taken from controlled laboratory and field studies and represent the average amount of drug required to provide maintenance anaesthesia for each target species. However the actual dose will be based on the response of the individual patient.

Dosing recommendations for maintenance of anaesthesia are as follows:

	DOGS		CATS	
	Un-premedicated	**Premedicated**	**Un-premedicated**	**Premedicated**
Dose for constant rate infusion				
mg/kg/hour	8 - 9	6 - 7	10 - 11	7 - 8
mg/kg/minute	0.13 - 0.15	0.10 - 0.12	0.16 - 0.18	0.11 - 0.13
ml/kg/minute	0.013 - 0.015	0.010 - 0.012	0.016 - 0.018	0.011 - 0.013
Bolus dose for each 10 minutes maintenance				
mg/kg	1.3 - 1.5	1.0 - 1.2	1.6 - 1.8	1.1 - 1.3
ml/kg	0.13 - 0.15	0.10 - 0.12	0.16 - 0.18	0.11 - 0.13

Where maintenance of anaesthesia is with the veterinary medicinal product for procedures lasting more than 5 to 10 minutes, a butterfly needle or catheter can be left in the vein, and small amounts of the veterinary medicinal product injected subsequently to maintain the required level and duration of anaesthesia. In most cases the average duration of recovery when using the veterinary medicinal product for maintenance will be longer than if using an inhalant gas as a maintenance agent.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

Acute tolerance to overdose has been demonstrated up to 10 times the recommended dose of 2 mg/kg in the dog (i.e. up to 20 mg/kg), up to 5 times the recommended dose of 5 mg/kg in the cat (i.e. up to 25 mg/kg) and up to 3 times the recommended dose in the rabbit (i.e. up to 15 mg/kg). These excessive doses delivered over 60 seconds caused apnoea and a temporary decrease in mean arterial blood pressure. The decrease in blood pressure is not life threatening and is compensated for by changes in heart rate. These animals can be treated solely by intermittent positive pressure ventilation (if required) with either room air or, preferably, oxygen. Recovery is rapid with no residual effects.

4.11 Withdrawal periods

Do not use in rabbits intended for human consumption.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: other general anaesthetics, alfaxalone.
ATCvet code: QN01AX05.

5.1 Pharmacodynamic properties

Alfaxalone (3-α-hydroxy-5-α-pregnane-11,20-dione) is a neuroactive steroid molecule with properties of a general anaesthetic. The primary mechanism for the anaesthetic action of alfaxalone is modulation of neuronal cell membrane chloride ion transport, induced by binding of alfaxalone to $GABA_A$ cell surface receptors.

5.2 Pharmacokinetic particulars

The volume of distribution after a single injection of clinical doses of 2, 5 and 5 mg/kg bw of alfaxalone in dogs, cats and rabbits is 2.4 L/kg, 1.8 L/kg and 3.6 L/kg, respectively. *In vitro* cat and dog hepatocyte studies show that alfaxalone experiences both Phase I (cytochrome P450 dependent) and Phase II (conjugation dependent) metabolism. Both cats and dogs form the same five (5) Phase I alfaxalone metabolites. The Phase II metabolites observed in cats are alfaxalone sulphate and alfaxalone glucuronide, while alfaxalone glucuronide is observed in the dog.

In cats, the mean terminal plasma elimination half-life ($t_{1/2}$) for alfaxalone is approximately 45 minutes for a 5 mg/kg dose. Mean plasma clearance for a 5 mg/kg dose is 25.1 ± 7.6 ml/kg/min.

In dogs, the mean terminal plasma elimination half-life ($t_{1/2}$) for alfaxalone is approximately 25 minutes for a 2 mg/kg dose. Plasma clearance for a 2 mg/kg dose is 59.4 ± 12.9 ml/kg/min.

In rabbits, the harmonic mean terminal plasma elimination half-life ($t_{1/2}$) for alfaxalone is approximately 44 minutes for a 5 mg/kg dose. Plasma clearance for a 5 mg/kg dose is 55.7 ± 13.3 ml/kg/min.

In dogs, cats and rabbits the elimination of alfaxalone demonstrates non-linear (dose-dependent) pharmacokinetics.

Alfaxalone metabolites are likely to be eliminated from the dog, cat and rabbit by the hepatic/faecal and renal routes, similar to other species.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropylbetadex
Sodium Chloride
Disodium Phosphate
Potassium Dihydrogen Phosphate
Sodium Hydroxide (for pH adjustment)
Hydrochloric Acid, Concentrated (for pH adjustment)
Water for Injections

6.2 Major incompatibilities

In the absence of compatibility studies, the veterinary medicinal product must not be mixed with other veterinary medicinal products.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
This product does not contain an antimicrobial preservative. Any solution remaining in the vial following withdrawal of the required dose should be discarded.

6.4 Special precautions for storage

Keep the container in the outer carton.

6.5 Nature and composition of immediate packaging

Cardboard box with one glass vial of 10 ml with a bromobutyl rubber stopper and aluminium cap.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste material derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Zoetis UK Limited
1st Floor, Birchwood Building
Springfield Drive
Leatherhead
Surrey
KT22 7LP

8. MARKETING AUTHORISATION NUMBER

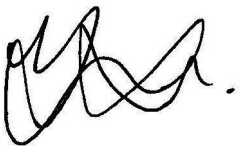
Vm 42058/4217

9. DATE OF FIRST AUTHORISATION

25 July 2017

10. DATE OF REVISION OF THE TEXT

August 2023



Approved: 14 August 2023