ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON <THE OUTER PACKAGE> <AND> <THE IMMEDIATE PACKAGE>

10 ml carton, 20 ml carton

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCES

1 ml contains:
Active substance:
alfaxalone 10 mg

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

10 ml
20 ml

5. TARGET SPECIES

Dog, cat, rabbit

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use.

8. WITHDRAWAL PERIOD(S)

Do not use in rabbits intended for human consumption.

9. SPECIAL WARNING(S), IF NECESSARY

This product is a sedative. In case of accidental injection seek medical attention immediately.

10. EXPIRY DATE

EXP. (month/year).
Shelf-life after first opening the container: 28 days.
Once broached use by …….

11. SPECIAL STORAGE CONDITIONS

Store below 25°C. Keep the vial in the outer carton in order to protect from light.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

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

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

16. MARKETING AUTHORISATION NUMBER(S)

Vm 42058/4218

17. MANUFACTURER'S BATCH NUMBER

Batch:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

10 ml vial, 20 ml vial

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

10 mg/ml

3. CONTENTS BY WEIGHT, BY VOLUME OR BY NUMBER OF DOSES

10 ml
20 ml

4. ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use.

5. WITHDRAWAL PERIOD(S)

Do not use in rabbits intended for human consumption.

6. BATCH NUMBER

Batch:

7. EXPIRY DATE

EXP. (month/year)

8. THE WORDS “FOR ANIMAL TREATMENT ONLY”

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET:

Alfaxan Multidose 10 mg/ml solution for injection for dogs, cats and pet rabbits
For animal treatment only

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

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

Manufacturers responsible for batch release:
Great Britain:
Zoetis Belgium SA
Rue Laid Burniat 1
1348 Lovain-La-Neuve
Belgium

Northern Ireland:
Jurox (Ireland) Limited
The Black Church
St. Mary's Place
Dublin
D07 P4AX
Ireland

Zoetis Belgium SA
Rue Laid Burniat 1
1348 Lovain-La-Neuve
Belgium

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENTS

Active substance:
Alfaxalone 10 mg/ml

Excipients:

Ethanol	150 mg/ml
Chlorocresol	1 mg/ml
Benzethonium chloride	0.2 mg/ml

Clear colourless solution for injection.

4. INDICATION(S)

As an induction agent prior to inhalation anaesthesia in dogs, cats and pet rabbits.
As a sole anaesthetic agent for the induction and maintenance of anaesthesia for the performance of examination or surgical procedures in dogs and cats.

5. CONTRAINDICATIONS

Do not use in combination with other intravenous anaesthetic agents.
Do not use on animals with hypersensitivity to the active substance or any other excipients.

6. ADVERSE REACTIONS

In clinical studies using Alfaxan Multidose, post induction apnoea, which was defined as the cessation of breathing for 30 seconds or more, was very common (more than 1 in 10 animals treated) in dogs and cats, and common (between 1 and 10 in 100 animals treated) in rabbits. 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.

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 (less than 1 animal in 10,000 animals treated).

In rabbits, defensive reactions (such as head-shaking, ear-flicking and backing away) are commonly observed during intravenous (marginal ear vein) administration and, therefore, administration of the product via a pre-placed catheter in the marginal ear vein is recommended. Premedication may also prevent these reactions. In a field study, these reactions were not observed when rabbits had been premedicated with medetomidine in combination with either butorphanol or buprenorphine.

If you notice any serious effects or other effects not mentioned in this leaflet, please inform your veterinary surgeon.

7. TARGET SPECIES

Dogs, cats and pet rabbits.

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

For intravenous use.

Induction of anaesthesia (dogs, cats and pet rabbits):
The induction dose of Alfaxan Multidose 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

In dogs, cats and rabbits, an intravenous catheter should be used to administer the product (please refer to Adverse Reactions section).

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 (dogs and cats):
Following induction of anaesthesia with Alfaxan Multidose, the animal may be intubated and maintained on Alfaxan Multidose or an inhalation anaesthetic agent. Maintenance doses of Alfaxan Multidose may be given as supplemental boluses or as constant rate infusion. Alfaxan has been used safely and effectively in both 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 a dog or cat. 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 Alfaxan Multidose for procedures lasting more than 5 to 10 minutes, a butterfly needle or catheter can be left in the vein, and small amounts of Alfaxan Multidose injected subsequently to maintain the required level and duration of anaesthesia. In most cases the average duration of recovery when using Alfaxan Multidose for maintenance will be longer than if using an inhalant gas as a maintenance agent.

9. ADVICE ON CORRECT ADMINISTRATION

In rabbits, an intravenous catheter should be used to administer the product due to the possibility of reactions (e.g. head-shaking and scratching at ear) during administration (please refer to Adverse Reactions section). The use of a preplaced catheter in dogs and cats is also recommended as best practice for anaesthetic procedures.

10. WITHDRAWAL PERIOD(S)

Do not use in rabbits intended for human consumption.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.
Store below 25°C. Keep the vial in the outer carton in order to protect from light.
Do not use this veterinary medicinal product after the expiry date which is stated on the label after “EXP”. The expiry date refers to the last day of that month.
Shelf life after first opening the container: 28 days.

12. SPECIAL WARNING(S)

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

Special precautions for use in animals
The safety of Alfaxan Multidose 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 Adverse Reactions 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 by slow intravenous injection (over a period of approximately 60 seconds) and not as a rapid dose.

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, which can occur secondary to respiratory depression or apnoea.

Especially when using higher doses of Alfaxan Multidose, 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.

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.

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. 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 Multidose. However, such reactions are not considered to be clinically significant.

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.

Use during pregnancy and lactation
The safety of Alfaxan Multidose 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 Dosage section) and the product was administered as recommended, to effect.

Interaction with other veterinary medicinal products
In dogs and cats, Alfaxan Multidose 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, Alfaxan Multidose 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 Alfaxan Multidose, necessitating cessation of further administration of Alfaxan Multidose when the required depth of anaesthesia has been reached. The use of one premedicant or a combination of premedicants often reduces the dose of Alfaxan Multidose 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 Alfaxan Multidose.

Also refer to Contraindications section.

Overdose
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.

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

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

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

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

August 2023

15. OTHER INFORMATION

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.
Pharmacokinetic particulars:
In cats following a single intravenous injection of alfaxalone at 5 mg/kg bw, the mean plasma elimination half-life ($t_{1/2}$) is approximately 45 minutes. Plasma clearance is 25 ml/kg/min. Volume of distribution is 1.8 L/kg.

In dogs following a single intravenous injection of alfaxalone at 2 mg/kg bw, the mean plasma elimination half-life ($t_{1/2}$) is approximately 25 minutes. Plasma clearance is 59 ml/kg/min. Volume of distribution is 2.4 L/kg.

In rabbits following a single intravenous injection of alfaxalone at 5 mg/kg bw, the mean plasma elimination half-life ($t_{1/2}$) approximately 46 minutes. Plasma clearance is 56 ml/kg/min. Volume of distribution is 3.6 L/kg.

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.

Pack sizes:
10 ml and 20 ml. Not all pack sizes may be marketed.

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.

Ireland: E-mail: customerservice@jurox.eu

Approved 24 August 2023