

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:

Alfaxalone 10 mg

Excipients:

Qualitative composition of excipients and other constituents	Quantitative composition if that information is essential for proper administration of the veterinary medicinal product
Ethanol	150 mg
Chlorocresol	1 mg
Benzethonium chloride	0.2 mg
Hydroxypropylbetadex	
Sodium Chloride	
Disodium Phosphate	
Potassium Dihydrogen Phosphate	
Sodium Hydroxide (for pH adjustment)	
Hydrochloric Acid, Concentrated (for pH adjustment)	
Water for Injections	

Clear colourless solution

3. CLINICAL INFORMATION

3.1 Target species

Dogs, cats and pet rabbits.

3.2 Indications for use for each target species

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.

3.3 Contraindications

Do not use in combination with other intravenous anaesthetic agents.

Do not use in cases of hypersensitivity to the active substance or any other excipients.

3.4 Special warnings

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

3.5 Special precautions for use

Special precautions for safe use in target species:

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 3.6 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.

In rabbits, oxygenation prior to administration of the veterinary medicinal 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.

In rabbits, an intravenous catheter should be used to administer the veterinary medicinal product due to the possibility of reactions (e.g. head-shaking and scratching at ear) during administration (please refer to section 3.6). The use of a preplaced catheter in dogs and cats is also recommended as best practice for anaesthetic procedures.

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/hypercapnia. 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 (SpO₂%) 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 the veterinary medicinal product. 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 veterinary medicinal 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 advice immediately and show the package leaflet or the label to the physician. The veterinary medicinal product may cause irritation if it comes into contact with the skin or eyes.

Rinse any splashes from skin or eyes immediately with water.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Dogs and cats:

Very common (>1 animal / 10 animals treated):	Apnoea ¹
Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Hyperactivity, vocalisation; Bradycardia, cardiac arrest; Convulsion, myoclonus, prolonged anaesthesia, tremor; Bradypnoea.

¹ Observed post induction. 44% of dogs and 19% of cats experienced post-induction apnoea in clinical studies; the mean duration of apnoea in these animals was 100 seconds in dogs and 60 seconds in cats. Endotracheal intubation and oxygen supplementation should therefore be employed.

Pet rabbits:

Common (1 to 10 animals / 100 animals treated):	Behavioural disorder ^{1,2} , head shake ² ; Ear flapping/twitching ² ; Apnoea ³ .
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¹ Manifested as backing away.

² During intravenous (marginal ear vein) administration and, therefore, administration of the veterinary medicinal 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.

³ Observed post-induction. The mean duration of apnoea in these animals was 53 seconds. Endotracheal intubation and oxygen supplementation should therefore be employed.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or its local representative or the national competent authority via the national reporting system. See package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

Pregnancy and lactation:

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 veterinary medicinal product should be used in pregnant animals according to the benefit-risk assessment performed by the responsible veterinarian. The veterinary medicinal 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 3.9) and the veterinary medicinal product was administered as recommended, to effect.

3.8 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 3.3.

3.9 Administration routes and dosage

Dogs, cats and pet rabbits: For intravenous use (IV).

Induction of anaesthesia (dogs, cats and pet rabbits):

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		PET 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 veterinary medicinal product (please refer to sections 3.5 and 3.6).

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 the veterinary medicinal product, the animal may be intubated and maintained on the veterinary medicinal product or an inhalation anaesthetic agent. 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 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 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.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

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.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

3.12 Withdrawal periods

Do not use in rabbits intended for human consumption.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QN01AX05.

4.2 Pharmacodynamics

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 GABAA cell surface receptors.

4.3 Pharmacokinetics

In cats following a single intravenous dose 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 dose 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 dose of alfaxalone at 5 mg/kg bw, the mean plasma elimination half-life ($t_{1/2}$) is 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.

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.

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

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

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

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf life after first opening the immediate packaging: 62 days.

5.3 Special precautions for storage

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

5.4 Nature and composition of immediate packaging

Cardboard box with one glass vial of 10 ml or 20 ml with a bromobutyl rubber stopper and aluminium cap.

Not all pack sizes may be marketed.

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

Medicines should not be disposed of via wastewater or household waste.
Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

{Name}

To be completed nationally

7. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: {DD/MM/YYYY}.

To be completed nationally

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

{DD/MM/YYYY}

To be completed nationally after conclusion of the procedure.

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (<https://medicines.health.europa.eu/veterinary>).

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

CARBOARD BOX OF 10 ml
CARBOARD BOX OF 20 ml

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Alfaxan Multidose 10 mg/ml solution for injection

2. STATEMENT OF ACTIVE SUBSTANCES

Each ml contains:
Alfaxalone 10 mg/ml

3. PACKAGE SIZE

10 ml
20 ml

4. TARGET SPECIES

Dogs, cats and pet rabbits.

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

Dogs, cats and pet rabbits: Intravenous use.

7. WITHDRAWAL PERIODS

Do not use in rabbits intended for human consumption.

8. EXPIRY DATE

Exp. {mm/yyyy}
Once broached use within 62 days.

9. SPECIAL STORAGE PRECAUTIONS

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

10. THE WORDS “READ THE PACKAGE LEAFLET BEFORE USE”

Read the package leaflet before use.

11. THE WORDS “FOR ANIMAL TREATMENT ONLY”

For animal treatment only.

12. THE WORDS “KEEP OUT OF THE SIGHT AND REACH OF CHILDREN”

Keep out of the sight and reach of children.

13. NAME OF THE MARKETING AUTHORISATION HOLDER

{Name or company name or logo name of the marketing authorisation holder}
To be completed nationally.

14. MARKETING AUTHORISATION NUMBERS

Number allocated by the Member State. To be completed nationally.

15. BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL OF 10 ml

VIAL LABEL OF 20 ml

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Alfaxan Multidose

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

Alfaxalone 10 mg/ml

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}

Once broached, use within 62 days.

B. PACKAGE LEAFLET

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

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

2. Composition

Each ml contains:

Active substance:

Alfaxalone 10 mg

Excipients:

Ethanol 150 mg

Chlorocresol 1 mg

Benzethonium chloride 0.2 mg

Clear colourless solution.

3. Target species

Dogs, cats and pet rabbits.

4. Indications for use

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 in cases of hypersensitivity to the active substance or any other excipients.

6. Special warnings

Special warnings:

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 safe use in the target species:

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 Adverse Events section 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 veterinary medicinal 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 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/hypercapnia. 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 (SpO₂%) 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 the veterinary medicinal product. 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 veterinary medicinal 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 medical advice immediately and show the package leaflet or the label to the physician. The veterinary medicinal product may cause irritation if it comes into contact with the skin or eyes.

Rinse any splashes from skin or eyes immediately with water.

Pregnancy and lactation:

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 veterinary medicinal product should be used in pregnant animals according to the benefit-risk assessment performed by the responsible veterinarian. The veterinary medicinal 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 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.

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.

Special restrictions for use and special conditions for use:

Major incompatibilities:

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

7. Adverse events

Dogs and cats:

Very common (>1 animal / 10 animals treated):
Apnoea ¹
Very rare (<1 animal / 10,000 animals treated, including isolated reports):
Hyperactivity, vocalisation; Bradycardia (slow heart rate), cardiac arrest; Convulsion, myoclonus (muscle spasm), prolonged anaesthesia, tremor; Bradypnoea (slow breathing rate).

¹ Observed post induction and defined as the cessation of breathing for 30 seconds or more. 44% of dogs and 19% of cats experienced post induction apnoea in clinical studies; the mean duration of apnoea in these animals was 100 seconds in dogs and 60 seconds in cats. Endotracheal intubation and oxygen supplementation should therefore be employed.

Pet rabbits:

Common (1 to 10 animals / 100 animals treated):
Behavioural disorder ^{1,2} , head shake ² ; Ear flapping/twitching ² ; Apnoea ³

¹ Manifested as backing away.

² During intravenous (marginal ear vein) administration and, therefore, administration of the veterinary medicinal 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.

³ Observed post induction and defined as the cessation of breathing for 30 seconds or more . The mean duration of apnoea in these animals was 53 seconds. Endotracheal intubation and oxygen supplementation should therefore be employed.

Reporting adverse events is important. It allows continuous safety monitoring of a product. If you notice any side effects, even those not already listed in this package leaflet, or you think that the medicine has not worked, please contact, in the first instance, your veterinarian. You can also report any adverse events to the marketing authorisation holder <or the local representative of the marketing authorisation holder> using the contact details at the end of this leaflet, or via your national reporting system: {national system details}.

8. Dosage for each species, routes and method of administration

Dogs, cats and pet rabbits: intravenous use.

Induction of anaesthesia (dogs, cats and pet rabbits):

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		PET 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 veterinary medicinal product (please refer to Adverse Events 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 ($\frac{1}{4}$) 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 the veterinary medicinal product, the animal may be intubated and maintained on the veterinary medicinal product or an inhalation anaesthetic agent. 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 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 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.

9. Advice on correct administration

In rabbits, an intravenous catheter should be used to administer the veterinary medicinal product due to the possibility of reactions (e.g. head-shaking and scratching at ear) during administration (please

refer to Adverse Events section). The use of a preplaced catheter in dogs and cats is also recommended as best practice for anaesthetic procedures.

10. Withdrawal periods

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 vial after Exp.

The expiry date refers to the last day of that month.

Shelf life after first opening the immediate packaging: 62 days.

12. Special precautions for disposal

Medicines should not be disposed of via wastewater <or household waste>.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any applicable national collection systems.

These measures should help to protect the environment.

13. Classification of veterinary medicinal products

Veterinary medicinal product subject to prescription.

14. Marketing authorisation numbers and pack sizes

To be completed nationally.

Pack sizes:

Cardboard box with one glass vial of 10 ml or 20 ml with a bromobutyl rubber stopper and aluminium cap.

Not all pack sizes may be marketed.

15. Date on which the package leaflet was last revised

{DD/MM/YYYY}

To be completed nationally

Detailed information on this veterinary medicinal product is available in the Union Product Database (<https://medicines.health.europa.eu/veterinary>)

16. Contact details

Marketing authorisation holder and contact details to report suspected adverse reactions:

To be completed nationally

Manufacturer responsible for batch release:

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

<Local representatives <and contact details to report suspected adverse reactions>:>

To be completed nationally

17. Other information

Pharmacodynamics:

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.

Pharmacokinetics:

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 ($t_{1/2}$) is 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.