

**IPAR**



**Publicly Available Assessment Report for a  
Veterinary Medicinal Product**

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

## PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.

The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

### I. SCIENTIFIC OVERVIEW

This was a generic 'hybrid' application in accordance with Article 13(3) of Directive 2001/82/EC, as amended. The reference product is Alfaxan 10 mg/ml Solution for Injection for Dogs and Cats which has been authorised in the UK since November 2006. This was determined a generic 'hybrid' application because changes to the target species with regard to the reference medicinal product have been made, by the inclusion of non-food pet rabbits. The final formulation of the product is quantitatively and qualitatively identical to the reference product with respect of the active substance. However, differences in the qualitative and quantitative composition of excipients are present due to the inclusion of a preservative system. The product is indicated as an induction agent prior to inhalation anaesthesia in dogs, cats and pet rabbits. It is also indicated as a sole anaesthetic agent for the induction and maintenance of anaesthesia for the performance of examination or surgical procedures in dogs and cats. For induction of anaesthesia the amount to be administered is taken from controlled laboratory and field studies and is the amount required to successfully induce anaesthesia in 9 out of 10 patients. For dogs this is 3 mg/kg bodyweight (unmedicated) or 2 mg/kg (premedicated). For cats 5 mg/kg bodyweight (unmedicated and premedicated), and for rabbits 5 mg/kg bodyweight (unmedicated) or 4 mg/kg (premedicated). For maintenance of anaesthesia in dogs and cats the product can be administered by supplemental boluses or constant rate infusion. Average dosage recommendations for anaesthesia maintenance are included in the SPC and are based on data taken from controlled laboratory and field studies. However, the actual dose should be based on the response of the individual patient.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto the market. It has been shown that the product can be safely used in the target species, any reactions observed are indicated in the SPC. The product is safe for the user, and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy of the product was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

### II. QUALITY ASPECTS

#### **II.A. Composition**

The product contains 10 mg/ml alfaxalone and the excipients ethanol, chlorocresol, benzethonium chloride, hydroxypropylbetadex, sodium chloride, disodium phosphate, potassium dihydrogen phosphate, sodium hydroxide, hydrochloric acid and water for injections.

The container/closure system consists of a glass vial of 10 or 20 ml with a bromobutyl rubber stopper and aluminium cap inside a cardboard box. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the presence of preservative are justified.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

#### **II.B. Description of the Manufacturing Method**

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of a simple process involving mixing and dissolution of components followed by pH adjustment, filling into sterilised vials and re-sterilisation via autoclave.

The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post-authorisation.

### **II.C. Control of Starting Materials**

The active substance is alfaxalone, an established active substance described in the British Veterinary Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

All excipients are described in the European Pharmacopoeia

#### **II.C.4. Substances of Biological Origin**

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

### **II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process**

Not applicable.

### **II.E. Control Tests on the Finished Product**

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification. Control tests on the finished product include those for: appearance, clarity, identity of active, identity of excipients, pH, content of active, content of excipients, degradation products, sterility and endotoxins.

### **II.F. Stability**

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

### **G. Other Information**

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.

Shelf life after first opening the immediate packaging: 28 days.

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

## **III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)**

As this was an application made in accordance with Article 13(3) of Directive 2001/82/EC as amended, and bioequivalence with the reference product has been demonstrated, there was no requirement for pharmacological or toxicological data in this section. Two in vivo bioequivalence studies comparing the final product formulation of the product with the reference product were presented and are discussed in Section 4.

### **User Safety**

A user risk assessment was provided in compliance with the relevant guideline which shows that the product is not expected to pose a risk to the user when used as recommended. The user risk assessment discussed the differences in formulation (inclusion of ethanol, chlorocresol and benzethonium as a preservative system).

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Therefore the following applicant's user recommendations are appropriate:

- 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.

**Environmental Safety**

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

**Phase I:**

The product will only be used in non-food animals and as a result environmental exposure will be low. A Phase II ERA was not required. The product is not expected to pose a risk to the environment when used as recommended.

**IV. CLINICAL ASSESSMENT**

This application was made as a generic 'hybrid' in accordance with Article 13(3) of Directive 2001/82/EC, as amended. As bioequivalence to the reference product has been demonstrated no clinical or pre-clinical data is required. The reference product was authorised for dogs and cats and the applicant also applied to include pet (non-food) rabbits as a target species. Additionally, the final formulation of the product differs from the reference product with regards to the inclusion of a preservative system (ethanol, chlorocresol and benzethonium chloride) which was not present in the reference product. The indications, warnings and advice for correct administration for cats and dogs are the same as for the reference product and an additional indication is for an induction agent prior to inhalation anaesthesia in pet rabbits. Bioequivalence studies comparing the final product formulation of the product with the reference product were presented and are discussed below. For the additional species, in consistency with the CVMP guideline (EMA/CVMP/EWP/117899/2004), pet rabbits are considered to be a minor species and extrapolation from the major species to this minor species can be accepted for pharmacodynamics.

**IV.I. Pre-Clinical Studies****Pharmacology**

The applicant has conducted two *in vivo* bioequivalence studies, one in dogs and one in cats. Both studies were randomised, two-period, cross-over study design with a 7 day washout period between doses. Twenty four healthy dogs or cats were randomly allocated to treatment groups using a ballot system. Each treatment group was randomly divided into two cohorts of 6 animals each. Animals were treated with the test or reference product at a dose of 3 mg alfaxalone/kg bodyweight for dogs and 5 mg/kg bodyweight for cats, intravenously via an IV catheter over a period of 60 seconds. Blood samples for all animals were collected pre-treatment and then post-treatment at 2, 5, 10, 20, 30, 45, 60, 120, 240, 360 and 480 minutes after the end of the test or reference product administration. Samples were also taken at 720 minutes post treatment in cats. Plasma alfaxalone concentrations were determined using HPLC-MS/MS[1] method. Pharmacokinetic parameters were calculated from the results obtained for alfaxalone for each animal at each dosing period using a mixed model analysis. The mixed model analysis was used to estimate the upper and lower limits of the 90% confidence interval for the ratio of treatment group means. A log transformation was used in the analysis of the pivotal variables. Equivalence was considered to have been achieved if the 90% confidence interval for the pivotal parameters  $AUC_{0-t}$  and  $C_{max}$  fell into the asymmetric  $\pm 20\%$  interval (0.80 - 1.25). The variables were subjected to an Analysis of Variance (ANOVA) or Analysis of Covariance (ANCOVA) evaluation. The lower and upper limits of the pivotal parameters all fell within the acceptance range of 80 – 125% and therefore bioequivalence between the test formulation and the reference formulation in dogs and cats has been demonstrated.

The applicant also carried out an *in vivo* dose finding and pharmacokinetic laboratory study in rabbits. This laboratory study investigated three IV doses (3, 4, 5 mg/kg alfaxalone) and three IM doses (6, 8, 10 mg/kg alfaxalone). The findings supported an optimal induction dose in rabbits of 5mg /kg alfaxalone administered intravenously.

**Tolerance in the Target Species**

The applicant carried out a pivotal safety study evaluating the safety of single and repeated doses in rabbits, including pharmacokinetic analysis. This was a three phase study involving healthy four month old rabbits. The first phase investigated the margin of safety after IV administration at 1X and 3X the proposed induction dose on two occasions. The second phase was a repeat dose study to investigate the pharmacodynamics, pharmacokinetics and safety after a 2X initial dose, followed by a 1X maintenance dose over 1 hours of anaesthesia. The third phase was a single dose study to characterise the pharmacokinetics after a single dose at 3X the proposed induction dose rate. Results showed the presence of significant dose-dependent respiratory depression following administration. Where apnoea occurred it was typically of short duration (<1 minute); however, this remains a clinically significant finding at the proposed induction dose. Mitigation in relation to similar adverse effects in dogs and cats is present in the SPC of the reference product and has been included with additional warnings relating to the use of the product in non-food rabbits. After repeated doses of the product to maintain anaesthesia, IPPV[2] was required in all rabbits. IPPV was also necessary in some rabbits after single 3X doses where the need for IPPV was triggered by elevated end-tidal  $CO_2$  levels. The high frequency of a requirement for IPPV in rabbits maintained using the test product suggested that the proposed product may not be suitable for maintenance of anaesthesia in rabbits. Findings support the presence of mild cardiovascular depression following use of the product. While heart rate and rhythm remained within

normal ranges during anaesthesia, a mild fall in blood pressure was observed after product administration. It is considered that the existing warnings in the SPC adequately mitigate for the risk of the product being used in an inappropriate population of animals at risk of adverse events due to cardiovascular depression. Behavioural responses such as ear scratching and head shaking were observed in rabbits during IV administration via the marginal ear vein. It is therefore recommended in the SPC that administration of the product in rabbits is via a pre-placed catheter

The applicant conducted two pilot safety and efficacy studies using a single induction of anaesthesia dose, one on dogs and one in cats. A pilot safety and efficacy study using a repeat dose for 1 hour anaesthesia was also carried out in cats. The formulation used in these studies contained 10 mg/ml alfaxalone and a preservative system and was compared with the reference product (un-preserved). Based on the results of these studies and other data submitted it was concluded that the development formulations were as safe and effective as the reference product and that the preservative system does not present additional risk to the cat and dog at the doses proposed for induction and maintenance of anaesthesia. A waiver for the requirement to conduct target species safety studies in the cat and dog based on bioequivalence to the reference product is therefore appropriate.

## V.II. Clinical Documentation

### Field Trials

Study title	A multicentre Clinical Trial in Rabbits Evaluating the Efficacy and Safety of Formulation RD0327 Administered Intravenously to Veterinary Patients for Induction of Anaesthesia.
Objectives	<p>The objectives of this study were to confirm the clinical efficacy and safety of alfaxalone 10 mg/ml plus preservatives in rabbits presenting as veterinary patients when administered:</p> <ol style="list-style-type: none"> <li>1. As the sole anaesthetic agent for induction and maintenance of general anaesthesia,</li> <li>2. In conjunction with pre-anaesthetic agents,</li> <li>3. For induction of general anaesthesia with subsequent maintenance using an inhalation anaesthetic.</li> </ol>
Test site(s)	Multi-centre, veterinary practices, third country.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	<p><u>IVP1:</u> RD0327 (alfaxalone 10 mg/ml). Induction dose of 5 mg/kg BW intravenously.</p> <p><u>IVP 2:</u> Alfaxan (alfaxalone 10 mg/ml) Induction dose of 5 mg/kg BW intravenously.</p>
Control product/placebo	No control treatment was used. However, as there is no EU-authorized product for this indication to act as a suitable comparator; the lack of a comparator is accepted.
Animals	<p>66 rabbits, male or female, 4 – 98 months old, 1.00 – 6.25 kg BW. Healthy (ASA category 1 or mild signs of systemic disease (ASA category 2)</p> <p>Inclusion criteria:</p> <ol style="list-style-type: none"> <li>1. Rabbits requiring anaesthesia (expected duration of approximately 60 minutes or less) for a veterinary procedure.</li> <li>2. Rabbits included by an Investigator in ASA class 1 or 2 based on history, physical examination and routine laboratory tests undertaken in the period up to seven days prior to anaesthetic administration.</li> </ol>

	<ol style="list-style-type: none"> <li>3. Biochemistry and haematology results in the period up to seven days prior to anaesthetic administration judged unremarkable by the Investigator and consistent with the ASA Class of the rabbit.</li> <li>4. Signed owner informed consent form.</li> </ol> <p>Exclusion criteria:</p> <ol style="list-style-type: none"> <li>1. Rabbits in ASA class 3 to 6.</li> <li>2. Rabbits that were otherwise considered by the Investigator to be unsuitable on assessment of results of physical examination, biochemistry or haematology.</li> <li>3. Previous enrolment in the study.</li> <li>4. Use of non-permitted concurrent medications. This would lead to exclusion of the rabbit's data from statistical analysis of affected efficacy and safety variables.</li> </ol> <p>5. If rabbits were removed from the study, their data could be excluded prior to statistical analysis with justification such as missing data.</p>
Randomisation	Non-randomised. This was acceptable given the objectives of the study and that the choice of premedication for anaesthesia must be personalised to the needs of the individual patient.
Blinding	Non-blinded.
Method	Client owned rabbits requiring general anaesthesia were administered one of the two test products following standard anaesthetic procedures. Rabbits were closely monitored until recovery from anaesthesia.
Variables recorded during the study.	<p>Successful induction of anaesthesia was defined as the point of successful endotracheal intubation.</p> <p><b>Pre-treatment (baseline):</b></p> <ul style="list-style-type: none"> <li>• Physical examination,</li> <li>• Bodyweight,</li> <li>• Serum biochemistry,</li> <li>• Haematology.</li> </ul> <p><b>Efficacy:</b></p> <ul style="list-style-type: none"> <li>• Duration of administration of IVP,</li> <li>• Time to onset of anaesthesia (time to intubation after product administration),</li> <li>• Total dose of IVP for induction,</li> <li>• Anaesthetic induction score,</li> <li>• Anaesthetic effectiveness score,</li> <li>• Duration of anaesthesia (time from intubation to extubation),</li> <li>• Time from extubation to head lift,</li> <li>• Time from extubation to first purposeful movement,</li> <li>• Anaesthetic recovery score.</li> </ul>

	<p><b>Safety:</b></p> <ul style="list-style-type: none"> <li>• Non-invasive blood pressure (NIBP),</li> <li>• Heart rate and rhythm,</li> <li>• Pulse rate,</li> <li>• Respiratory rate,</li> <li>• Mucosa colour,</li> <li>• Rectal temperature,</li> <li>• Blood oxygen saturation of haemoglobin,</li> <li>• End tidal CO<sub>2</sub> (ETCO<sub>2</sub>),</li> <li>• Duration of immediate post-induction apnoea (IPIA = breathing cessation &gt; 30 seconds),</li> <li>• Response to IVP injection and injection site evaluation.</li> </ul>
Statistical method	<p>The following four outcome variables were evaluated to investigate efficacy objectives:</p> <ul style="list-style-type: none"> <li>• Total dose of IVP for induction</li> <li>• Anaesthetic induction score</li> <li>• Anaesthetic effectiveness score</li> <li>• Anaesthetic recovery score.</li> </ul> <p>Descriptive statistics for these variables were reported treatment group. Comparative analysis of variables by treatment group was performed using Stata.</p>
RESULTS	
Participant flow	<p>69 rabbits were evaluated. 66 rabbits were enrolled on the trial. 6 rabbits were removed from the study. One rabbit died during the study. Rabbits were divided into five groups (Group 1 unpremedicated, Groups 2-5 premedicated). 50 rabbits were treated with the proposed products (RD0327) and 10 rabbits were treated with the reference product (Alfaxan)</p>
Adverse events	<p>One adverse event (cardiac arrest, resulting in death) was recorded during the study. This occurred following administration of RD0327. The underlying cause of this event is unclear, although clearly precipitated by the administration of the proposed product. However, the respiratory depressant effects of alfaxalone are well established, and a plausible association between the administration of this active substance and the described adverse events can be made. Despite this event it can be concluded that the proposed product was used without serious adverse events in most rabbits treated and the statements included in sections 4.5 and 4.6 of the SPC adequately mitigate the risk of life-threatening respiratory depression or hypoxaemia.</p>
DISCUSSION	<p>General anaesthesia was successfully induced with both test products in all 60 rabbits. Measured variables described above were monitored and on average the data collected for physiological parameters during anaesthetic induction, maintenance and recovery were within acceptable clinical limits for healthy rabbits undergoing general anaesthesia. Only one adverse event occurred: cyanosis and cardiac arrest in a rabbit which subsequently died which is discussed above. The dose required to achieve induction of anaesthesia was</p>

	higher in unpremedicated rabbits compared to premedicated rabbits. The proposed dosage of 5 mg/kg for unpremedicated rabbits and 4 mg/kg for premedicated rabbits is supported by the study results. Duration of anaesthesia lasted no more than one hour for a majority of procedures with anaesthetic quality scores similar between RD0327 and Alfaxan. All anaesthetic cases were maintained with isoflurane with oxygen and therefore neither products was the sole agent for induction and maintenance of general anaesthesia as originally planned in the study objectives. Behavioural reactions were observed during administration of the product which may indicate pain during injection. A warning has been added to section 4.6 of the SPC recommending the use of a pre-placed IV catheter to mitigate this. Results and statistical analysis support the safety and efficacy of the proposed product in rabbits both in combination with pre-medication and alone.
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[1] HPLC-MS/MS – High Performance Liquid Chromatography with tandem Mass Spectrometric detection.

[2] Intermittent positive pressure ventilation

## V. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics the benefit/risk profile of the product is favourable.