Veterinary Medicines Directorate

**United Kingdom**
**Veterinary Medicines Directorate**
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**NATIONAL PROCEDURE**

# PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

## Alfaxan 10 mg/ml Solution for Injection for Dogs, Cats and Pet Rabbits

**Date Created: September 2017**

# MODULE 1

## PRODUCT SUMMARY

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| Name, strength and pharmaceutical form | Alfaxan 10 mg/ml Solution for Injection for Dogs, Cats and Pet Rabbits |
| Applicant | Jurox (UK) Limited<br>Second Floor, Richmond House<br>105 High Street<br>Crawley<br>West Sussex<br>RH10 1DD<br>United Kingdom |
| Active substance | Alfaxalone |
| ATC Vetcode | QN01AX05 |
| Target species | Cats, Dogs and Rabbits |
| Indication for use | As an induction agent prior to inhalation anaesthesia in cats, dogs and non-food rabbits.<br><br>As a sole anaesthetic agent for the induction and maintenance of anaesthesia for the performance of examination or surgical procedures in cats and dogs. |

# MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

# MODULE 3

## PUBLIC ASSESSMENT REPORT

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| Legal basis of original application | A generic 'hybrid' application in accordance with Article 13 (3) of Directive 2001/82/EC as amended. |
| Date of conclusion of the procedure | 25/07/2017 |

## I. SCIENTIFIC OVERVIEW

This application was submitted in accordance with Article 13 (3) of Directive 2001/82/EC, as amended by 2004/28/EC (a 'hybrid' application). The reference product is Alfaxan 10 mg/ml Solution for Injection for Dogs and Cats, marketed by Jurox (UK) Ltd., which has been authorised in the UK since 2006. The proposed product was determined a generic 'hybrid' application because the MAH has proposed a new target species, non-food rabbits.

The product is indicated for use as an induction agent prior to inhalation anaesthesia in cats, dogs and non-food rabbits and as a sole anaesthetic agent for the induction and maintenance of anaesthesia in cats and dogs.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released on 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.[1] 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 [2] 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.

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

## II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

### *II.A. Composition*

The product contains 10 mg/ml alfaxalone and the excipients hydroxypropylbetadex, sodium chloride, disodium phosphate, potassium dihydrogen phosphate, sodium hydroxide (for pH adjustment), hydrochloric acid, concentrated (for pH adjustment) and water for injections

The container/closure system consists of a glass vial with a bromobutyl rubber stopper. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the absence of a 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 filtering, mixing and sterilising process.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

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

The active substance is alfaxalone, an established active substance described in the British Veterinary Pharmacopoeia. Some additional tests for impurities and residual solvents have been added. 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.

Hydroxypropylbetadex, sodium chloride, disodium phosphate anhydrous, potassium dihydrogen phosphate, sodium hydroxide, hydrochloric acid concentrated and water for injections in bulk used in the manufacture of the product are comply with the requirements of the relevant European Pharmacopoeia monographs

### *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, pH, degradation products sterility, identification and assay of alfaxalone.

## *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*

Keep the container in the outer carton.

Shelf life of the veterinary medicinal product as packaged for sale: 5 years.
This product does not contain an antimicrobial preservative. Any solution remaining in the vial following withdrawal of the required dose should be discarded.

# III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

As this application was for a generic ' hybrid' in accordance with article 13 (3) of Directive 2001/82/EC no pharmacological or toxicological data were required.

## *User Safety*

A user risk assessment was provided in compliance with the relevant guideline which shows that there is a possibility of accidental self-injection and dermal exposure.

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.

The product will only be used in non-food animals and as a result environmental exposure will be low. For these reasons assessment stopped at Phase I. A Phase II ERA was not required.

## *Withdrawal Periods*

Withdrawal period advice has been included on the SPC to ensure that the product is not used in rabbits intended for human consumption.

# IV. CLINICAL DOCUMENTATION

Cats and Dogs
As this application was for a generic 'hybrid' in accordance with article 13 (3) of Directive 2001/82/EC bioequivalence studies comparing the proposed and reference products in cats and dogs were therefore not required. To demonstrate bioequivalence between the proposed product and reference product, in no-food rabbits, two bioequivalence studies, one in cats and one in dogs, were provided the results from which are briefly discussed under 'pharmacokinetics' below.

In accordance with article 13 of Directive 2001/82/EC, as amended, no preclinical or clinical studies in cats and dogs are required for this application. Claims in cats and dogs previously accepted for the reference product are therefore accepted.

Rabbits
The majority of the data submitted with Part IV are provided in support of the new target species, non-food rabbits. This is a minor species and therefore the CVMP 'Guideline on efficacy and target animal safety data requirements for veterinary medicinal products intended for minor uses or minor species' (EMEA/CVMP/EWP/117899/2004) was taken into consideration during assessment, for this type of application, some redacted information is permitted.

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

### *Pharmacology*

**Pharmacodynamics**
The pharmacodynamic activity of alfaxalone on GABAA cell surface receptors and its anaesthetic action via modulation of neuronal cell membrane chloride ion transport in cats and dogs can be extrapolated from the reference product. For non-food rabbits, consistent with the CVMP guideline, extrapolation from the major species to this minor species can also be accepted for 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.

**Pharmacokinetics**
The applicant has collected data supporting the pharmacokinetics of alfaxalone in the proposed product during two non-GLP pre-clinical studies, in order to support the information provided in the SPC for rabbits:

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 (t1/2) 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 (t1/2) 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 (t1/2) 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.

### *Tolerance in the Target Species*

The applicant has conducted a controlled target animal tolerance study using multiples of the recommended dose in the target species rabbit. All doses were administered intravenously on two occasions with additional boluses to maintain anaesthesia. A field trial was also conducted which supported the adverse effect information included in the SPC.

Adverse effects consisting of respiratory depression, cardiovascular depression, fall in blood pressure were seen at the recommended dose. Additional behavioural responses were observed including head-shaking and ear-scratching.

The product literature accurately reflects the type and incidence of adverse effects which might be expected.

## *IV.II. Clinical Documentation*

### *Laboratory Trials*

The applicant has conducted a field trial to support the dose confirmation data provided in the bioequivalence and safety studies which confirms that a dose of 5 mg/kg (for non–premedicated rabbits) or 4 mg/kg (for premedicated rabbits) are effective for the induction of anaesthesia.

### *Field trial:*

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| 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 | To confirm clinical efficacy and safety of proposed product. |
| Test site(s) | Multi-centre, veterinary practices. |
| Compliance with Regulatory guidelines | Good Clinical Practice (GCP) |
| Test Product | Alfaxalone 10 mg/ml and reference product at various dose rates to induce anaesthesia. |
| Control product/placebo | No control. |
| Animals | 66 privately owned rabbits aged between 4 – 98 months. 4 groups.<br>Weight: 1 – 6.25 kg<br>Two groups: Healthy or mild systemic disease.<br>Inclusion Criteria<br>Needing anaesthesia for a veterinary procedure<br>Blood test results within specified range.<br>Owner's consent.<br>Exclusion Criteria<br>Previous enrolment.<br>Non – permitted concurrent medicines.<br>Unsuitable candidates at pre-trial clinical assessment |
| Outcomes/endpoints | Time to onset of anaesthesia, total dose needed for induction and duration of anaesthesia. |
| Randomisation | Not randomised |
| Blinding | Not blinded |
| Method | Each rabbit was anaesthetised once.<br>Amount of test product required and time to onset of anaesthesia was recorded. |
| Statistical method | Comparative statistics:<br>The following four outcome variables were evaluated to investigate efficacy objectives:<br>- Total dose of IVP for induction,<br>- Anaesthetic induction score,<br>- Anaesthetic effectiveness score,<br>- Anaesthetic recovery score.<br>Descriptive statistics for these variables were reported by treatment group. Comparative analysis of variables by treatment group was performed using Stata. |
| RESULTS | |
| Outcomes for endpoints | The dose required to achieve induction of anaesthesia was higher in non-premedicated rabbits than in premedicated rabbits although a between-group comparison could only show a statistically significant difference ($p = 0.002$) between 2/4 groups. |

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| | The time to onset of anaesthesia varies significantly between groups and in most cases occurred within 5 minutes of the end of treatment administration.<br>The duration of anaesthesia in rabbits administered with the test product ranged from 32-52 minutes, however the test product was never solely used for the maintenance of anaesthesia..<br>The anaesthetic effectiveness and anaesthetic recovery scores were not statistically significant. |
| DISCUSSION | The results of this clinical trial do confirm the field efficacy and safety of both formulation RD0327 (preserved) and Alfaxan Anaesthetic Injection (unpreserved) when administered “to effect” (up to a total dose of 5 mg alfaxalone/kg BW) by veterinary clinicians to non-premedicated and premedicated rabbits for the induction of general anaesthesia with subsequent maintenance using an inhalational anaesthetic under practical use conditions. |

## 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 products is favourable.

# MODULE 4

## POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

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