IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

ALFAXAN 10 mg/ml solution for injection for dogs and cats.

PRODUCT SUMMARY

EU Procedure number	IE/V/0590/001 (formerly UK/V/0278/001)
Name, strength and pharmaceutical form	ALFAXAN 10 mg/ml solution for injection for dogs and cats
Active substances(s)	Alfaxalone
Applicant	Jurox (UK) Limited Second Floor, Richmond House 105 High Street Crawley West Sussex RH10 IDD United Kingdom
Legal basis of application	Full application (Article 12(3) of Directive No 2001/82/EC)
Date of Authorisation of original MRP	27 February 2008 (UK) 16 May 2008 (IE)
Date product first authorised in the Reference Member State (MRP only)	23 November 2006
Target species	Cats, Dogs
Indication for use	As an induction agent prior to inhalation anaesthesia. As a sole anaesthetic agent for the induction and maintenance of anaesthesia for the performance of examination or surgical procedures.
ATCvet code	QN01AX05
Concerned Member States	Original procedure: Ireland (now RMS)

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

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; the slight 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

A. Composition
The product contains alfaxalone and excipients hydroxypropylbetadex, sodium chloride, disodium phosphate anhydrous, potassium dihydrogen phosphate, sodium hydroxide, hydrochloric acid, concentrated and water for injections.

Alfaxan is packaged in clear, colourless, neutral glass (Type 1) vials. The capacity is 13ml, but the vial holds 10ml of product. The vials are closed with fluoropolymer-coated grey bromobutyl rubber closures secured with an aluminium collar. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation is justified.

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

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

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

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

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

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

E. Control on intermediate products

There are no intermediate products.

F. 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.

G. 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.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

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

Special precautions for storage:
Do not freeze. Keep the container in the outer carton.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The company has mainly relied on published literature relating to a human product to support their laboratory studies. The human product contains a 3:1 combination of alfaxalone and alfadolone and so the results can be applied to Alfaxan. Alfaxalone is a neuroactive steroid with the properties of a non-volatile general anaesthetic.

The company has provided details with respect to the pharmacodynamics and has provided three GLP compliant studies on the pharmacokinetics of alfaxalone. The data are considered acceptable given the nature of the product and the intended route of administration.

For pharmacokinetics it was concluded that distribution and clearance of alfaxalone after intravenous administration is rapid in the dog, cat, rat and humans. Elimination is primarily by the biliary and urinary routes, predominantly as glucuronidated metabolites.

Toxicological Studies

Single and repeat dose toxicity

The company has provided published studies relating to single dose and repeat dose toxicity of alfaxalone. Some of these studies were conducted using the human product. These results can be used for Alfaxan as the composition of the human product contains the same active substance as Alfaxan. The company has also provided GLP compliant studies which showed that intravenous administration of Alfaxan was shown to be safe and effective at 5, 15 and 25 mg/kg doses in cats and at 2, 6 and 10mg/kg doses in dogs when repeated every other day on three occasions. No adverse effects of repeated administration were seen over this period of time in any of the parameters measured.

Alfaxan was shown to have cardio respiratory depressing effects, most notably in the post induction period, the most significant of which were on blood pressure and SpO2. Anaesthetic duration period and duration of non-responsiveness to noxious stimuli were of a clinically relevant timescale and were dose dependant, whilst quality of induction, maintenance and recovery were deemed good. The "no observed adverse effect level" (NOAEL) for the cat was 5x (=25mg/kg) and for the dog was 10x (=20mg/kg).

Reproductive toxicity

The company has provided published studies relating to reproductive toxicity of alfaxalone conducted using the human product. The studies showed that Alfaxan had no effect on growth or fertility of animals when administered prior to or throughout pregnancy. It did not cause premature parturition when administered in larger doses to animals at the end of pregnancy. The offspring of all the treated animals were reported to develop normally and were fertile at maturity.

Alfaxan was also given (as the human product) intravenously every 8-12 hours of the final one to three days of pregnancy, and an additional dose was given if the onset of delivery was observed and the animals were live. There were no adverse effects observed in newborn animals whose mothers had been administered injections in the final days of pregnancy. In the three animals treated during delivery, offspring born prior to injection were all alive, most born afterwards were either dead on delivery or died within the hour. Alfaxan was also administered intravenously to pregnant animals daily throughout pregnancy with no effects on maternal bodyweight, gestation length, litter size or neonatal survival.
Alfaxan, when administered as the human product, also had no effect on foetal growth or survival, and no treatment related malformations were reported.
Due to these data the following statement has been included on the SPC.

The safety of the veterinary medicinal product has not been established in cases where pregnancy is to be continued or during lactation. Its effects upon fertility have not been evaluated. However, studies using alfaxalone in pregnant mice, rats and rabbits have demonstrated no deleterious effects on gestation of the treated animals, or on the reproductive performance of their offspring. The product should be used in pregnant animals according to the risk-benefit assessment performed by the veterinarian.

Mutagenicity

The company has provided three GLP compliant studies on the mutagenicity of Alfaxan. The studies concluded that there were no mutagenic effects observed for the active substance alfaxalone, over a range of concentrations, in any of the five tester bacterial strains used with or without metabolic activation. Alfaxalone also did not induce chromosomal aberrations under test conditions. It was concluded that the active substance and formulation possessed no mutagenic potential.

Carcinogenicity
Due to there being no reports of carcinogenicity in animals in published literature or pharmacovigilance data, and no pre-neoplastic lesions observed in the repeat dose toxicity or target species safety studies, no further studies are required for Alfaxan. The results of the mutagenicity studies supported this.

Other Studies
Special studies (e.g. specific target organ toxicity)
The company considered that specific ocular and dermal irritation studies were unnecessary due to the pattern of formulation, and that the active substances and excipients are well known in human and veterinary pharmaceutical preparations. The company did submit a dermal sensitisation study which showed that Alfaxan is not a potential skin sensitizer.

Observations in Humans
Pharmacokinetics:
The company submitted studies that had been conducted using the human product on human patients undergoing a variety of surgical procedures. The patients who were observed ranged from being healthy to having various illnesses such as jaundice and chronic renal disease. The studies showed no adverse effects in any of the patients, but age was shown to reduce the effective dose values of the active substance alfaxalone. Also hepatic conjugation with glucuronic acid is important in the excretion of alfaxalone, and therefore in patients with chronic liver disease Alfaxan may be excreted at a slower rate than healthy patients.

Effects on the foetus:
The company submitted three studies that had investigated the effect of the human product on human births. One study focused on caesarean deliveries and the human product was the sole anaesthetic agent used. The authors concluded that the human product crosses the placental barrier and, at high doses, will achieve levels that may cause significant neonatal depression.

Another study compared the human product with another human anaesthesia when used for caesarean deliveries. The study found that there were no differences between the two anaesthetics in terms of delivery intervals, maternal to foetal blood gas gradients and Apgar[1] score.

A study used the human product to induce anaesthesia and maintained it by using other unrelated agents in human patients under going caesarean delivery. Maternal blood gas analysis showed mild respiratory alkalosis associated with mild metabolic acidosis that appeared to increase during anaesthesia. Umbilical cord blood-gas analysis showed mild foetal respiratory acidosis associated with significant foetal acidosis. Modified Apgar scores indicated that a few infants showed either mild or severe foetal depression at two minutes after delivery.

Overdose:
The company submitted two examples of accidental overdose in humans, and in each case no long term effects were reported.

Microbiological Studies
These studies were not applicable to this product as it has no known antimicrobial activity.

Studies on metabolites, impurities, other substances and formulation:
There are no specific issues relating to the known metabolites or impurities of the active substance alfaxalone. The excipients are all commonly used substances of parenteral formulations used for human and veterinary medicines. Therefore no studies are required under this section.

User Safety
The company provided a user risk assessment along with some additional data. Significant oral ingestion is considered to be unlikely given the intended use of the product and the low volume in each vial. Dermal and ocular exposure from splashing as a result of breakage of the vial or during administration is possible, but again would only be to a small volume. The formulation is not a potential sensitizer.

Accidental injection would most likely result in intradermal, subcutaneous or intramuscular exposure; accidental intravenous administration is far less likely. Consequently accidental exposure is unlikely to present a significant risk.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

[1] A practical method of evaluating the physical condition of a newborn infant shortly after birth (Activity (muscle tone), Pulse, Grimace (reflex irritability), Appearance (skin colour), Respiration)

IV. CLINICAL ASSESSMENT

Pharmacology

Pharmacodynamics

The company has given published literature references to support this section, which discuss the binding properties of the active substance alfaxalone. The published literature describes how the anaesthetic action of alfaxalone is achieved by its binding to receptors for inhibitory neurotransmitters in the nervous system, and also identifies that alfaxalone and benzodiazepines have different binding sites on the receptors of certain neurotransmitters. Alfaxalone has been shown to have an effect on the nervous system by modifying the sensitivity of nerve responses. Also if certain receptors on the neurotransmitters are blocked then so is the action of alfaxalone.

The published literature also describes the secondary pharmacodynamic effects of alfaxalone and its effects on nicotinic, glycine, and noradrenalin activity. Even though alfaxalone is a steroid there is evidence in the references that it does not bind to other steroidal or behavioural receptor sites.

Pharmacokinetics

The company submitted studies to investigate the various pharmacokinetic aspects of Alfaxan.

One study showed that when alfaxalone, the active substance, was administered intravenously to dogs it provided effective anaesthesia. The data presented suggested that based on clearance levels, anaesthesia may be safely maintained by continual infusion, by pump or by incremental doses, as Alfaxan is rapidly cleared from the body. The pharmacokinetic parameters of alfaxalone after a single dose administration do not differ between genders or between 2mg/kg and 10mg/kg dose rates.

Another study concluded that Alfaxan provided safe and stable anaesthesia for cats at both 5mg/kg and 25mg/kg doses for durations of less than three hours, provided that ventilatory support was provided for the higher dose rate group. Non-linear pharmacokinetics were observed resulting in greater than expected drug exposure, as well as a greater than expected dose proportional duration of action in the 25mg/kg dose group. Clearance was significantly dose dependant, resulting in an increased mean half-life: from 45 minutes at 5mg/kg to 77 minutes at 25 mg/kg.

A study showed that body temperature dropped during prolonged anaesthesia, which is to be expected, and all other parameters remained within acceptable limits at all times. The results also showed that Alfaxan is safe and effective for maintenance of anaesthesia in cats when repeatedly administered at the recommended doses, and there is no accumulation at these levels.

A study was conducted to investigate the in vitro metabolism of alfaxalone in dogs and cats. The phase I metabolites produced by the dogs and cats were identical, but produced in different concentrations. This is attributable to the different enzyme joining speeds in the two species at higher alfaxalone concentrations. The phase II metabolites produced differed considerably between the two species. Alfaxalone metabolites are likely to be eliminated from the dog and cat by hepatic/faecal and renal routes, similar to other species

Tolerance in the Target Species of Animals

Dogs

The company has conducted studies into the tolerance of Alfaxan in dogs. One study found that slight respiratory depression was noted when Alfaxan was administered at 10mg/kg, leading to a transient period where SpO_2 dropped below 90%. Induction was smooth and intubation was easily achieved. Animals recovered well with little or no agitation and no cardiac arrhythmias. There were no abnormal electrocardiogram (ECG) readings.

Another study showed that Alfaxan has only mild effects on cardiovascular parameters and most of the physiological changes seen can be attributed to actions of the premedicant used. There was a mild depression with Alfaxan, especially immediately post induction. This was no more than may be expected with most injectable anaesthetics, and it was not clinically significant. The results also showed that the dose of Alfaxan required is reduced by the use of a premedicant. During the course of this study there were also no arrhythmias[1] recorded.

One study showed that Alfaxan produced safe and effective anaesthesia at clinical and higher doses. However, at the higher dose rates ventilatory support may be required, as apnoea[2] is commonly encountered.

Another study demonstrated that at doses up to 3 times the recommended levels, Alfaxan is safe to administer to adult dogs as a single injection. Physiological changes observed were mild and not clinically relevant, with the exception of post induction apnoea. There was no significant biochemical, haematological gross or microscopic pathological changes found. The post induction apnoea was only clinically significant at the highest dose (10mg/kg) when, SpO_2 dropped to 81% for the first 2-4 minutes post induction in the male dogs breathing room air.

A study confirmed Alfaxan to be safe and effective for anaesthetic induction and maintenance of dogs. Premedicant drug interactions were also confirmed, and these reduced the induction and maintenance in dogs. However one premedicant used, midazolam, caused an increase in the dose of Alfaxan required for induction and maintenance, and produced a poorer, but still acceptable, recovery.

Two studies were conducted into the possibility of histamine release. The first study clearly demonstrated that histamine release is not likely to be a problem in dogs with the formulation used in Alfaxan, in doses up to 30mg/kg. Both studies showed that the problematic release of histamine, which has occurred in the past, was related to the presence of an additional substance not used in Alfaxan.

Another study compared Alfaxan with another anaesthetic for induction of anaesthesia. The products were shown to be broadly similar with few physiological changes of a clinically significant level in either case.

Cats

The company has conducted studies into the tolerance of Alfaxan in cats. One study showed that the clearance of alfaxalone from an animal was dose dependent, and total clearance from an animal was rapid at both 5mg/kg and 25mg/kg dose rates. The results also showed that Alfaxan has minimal physiological effects when administered at 1x and 5x the recommended dose rates, except that severe respiratory suppression occurs at the higher dose rate. The study showed that Alfaxan may be used to maintain anaesthesia for >3 hours safely.

Another study found that Alfaxan was shown to be safe and effective when used in combination with four commonly used premedicants in adult animals. The four premedicants used were acepromazine, medetomidine, butorphanol and midazolam, each at their maximum labelled or recommended premedication doses. Any physiological effects of Alfaxan were minimal and limited to respiratory suppression, which was not clinically significant. The duration of anaesthesia and recumbency was short when the premedicants butorphanol and midazolam were used, but extended 2-6 fold when acepromazine or medetomidine were used. Induction, maintenance and recovery were smooth and uneventful, though midazolam did cause an increased sensitivity to external noise during recovery. Premedication reduced the total volume of Alfaxan required by approximately 27%, but did not alter the duration over which the dose should be given.

One study demonstrated that the maximum clinically recommended dose rate for cats of 5 mg/kg is well tolerated when used as a single dose for induction. It was also shown that a 10x induction dose is invariably terminally damaging to the animal and should not be used. It also highlights the potential risks associated with the use of Alfaxan in cats, where clearance from the animal is reduced; this is associated with hepatic or renal compromise or concurrent medication.

A study showed that, for a single induction dose of Alfaxan at 1, 3 or 5x the recommended dose rate, on repeated occasions 48 hours apart, there were only minimal physiological changes noted. The main one was respiratory suppression particularly at the higher dose rate, but this was not clinically significant. There were no significant biochemical, haematological, gross or microscopic pathological changes found.

A study showed that Alfaxan causes only minimal physiological effects when used both for induction as a single dose 5mg/kg, and for maintenance using a reduced dose of 2mg/kg on four consecutive occasions, resulting in an average anaesthesia time of 2 hours. There was no evidence of accumulation of Alfaxan when doses were repeated, when times between required doses remained approximately constant.
One study confirmed the safety and efficacy of Alfaxan as both an induction and a maintenance agent. All premedicant combinations worked well, although midazolam was the poorest. All other premedicants used caused a reduction in the total amount of Alfaxan required for induction and a prolonged recovery period.

The results of another study were only considered as supportive evidence as the formulation of the test product was not exactly the same as the proposed product. The study provided evidence on the comparative safety of Alfaxan when used as a single dose for induction of anaesthesia at 1, 2, 4 and 6x the recommended dose. It also showed that while 1 and 2x dose rates are safe with few physiological changes, there was serious respiratory depression with related reductions on SpO_2 and clinically significant reductions in arterial pressure, which occurred at 4x and 6x dose rates. The study also showed that histamine release is negligible when Alfaxan is used, compared to other formulations of alfaxalone.

The company also submitted pharmacovigilance data to support Alfaxan's tolerance in target species studies. This pharmacovigilance data was for Alfaxan-CD RTU based on adverse event reports made to the company from 1999 to May 2005 or to the Australian Pesticides and Veterinary Medicines Authority from 1999 to May 2003. This product can be compared to Alfaxan as it has the same formulation. A tabulated summary of all cases was prepared capturing the essential details of all cases reported, and attempted to ascertain the likelihood of Alfaxan being the cause of the reported reaction. This was then compared to the sales figures of Alfaxan over the same period in order to estimate the proportion of cases treated with Alfaxan that may be experiencing adverse reactions. The data showed that Alfaxan has an acceptable safety profile in cats and dogs when used as recommended, and presents minimal risk to the patient and the human handlers

IV.B Clinical Studies

The company has also conducted field trials.
One field trial was conducted to confirm the clinical safety and efficacy of Alfaxan in dogs when administered as the sole anaesthetic agent for induction and maintenance, in conjunction with commonly used premedicants, and when used for induction only and subsequent maintenance by inhalation anaesthesia. The results used Rapinovet, an already licensed anaesthetic, as a positive control. A varied range of animals were used, in regards to age, sex, breed, disease status etc, to test Alfaxan in this trial. The results of the study showed that there were no directly related adverse effects, and the previously attributed low depression of cardio respiratory parameters was confirmed. A smooth induction, stable maintenance and quiet recovery were also established and confirmed. Post induction apnoea was encountered and it was concluded to be of a similar level to that found using Rapinovet as an induction agent, and provided that appropriate support was available, was not detrimental to the anaesthetic. Midazolam was shown to not interact well with Alfaxan when used as the sole premedicant.

A study was conducted to evaluate the clinical efficacy of Alfaxan CD-RTU in dogs when used at several clinics. The formulation used for this study was different from that of the proposed product. The potential dose rates suggested at the start of the study were too high, and that dosing too rapidly induced apnoea. The actual dose rates required for premedicated and unpremedicated animals were 1-2mg/kg. This should be administered slowly over at least 20-30 seconds and not as a rapid bolus[3], in order to reduce the risk of apnoea. Incremental dosing of 2.1-8.8mg/kg was suitable for maintenance of anaesthesia. Alfaxan-CD RTU was shown to be safe and effective as an intravenous induction and maintenance agent.

A study was conducted to confirm the efficacy and safety of Alfaxan in cats anaesthetised at 10 veterinary hospitals, compared to cats anaesthetised with the already licensed anaesthetic Rapinovet. Alfaxan was shown to be safe and effective in combination with a range of commonly used premedicants, as both induction and maintenance agent in cats undergoing an array of veterinary procedures. Physiological changes induced by Alfaxan use were minimal, stable and clinically acceptable, with the provision that oxygen supplementation should be available in case of apnoea. The incidence was similar to that seen with Rapinovet, and was clinically acceptable. The incidence of apnoea was reduced by slow administration of the drug. Quality of anaesthesia was good to excellent in most cases, but the premedicant midazolam did not interact as well with Alfaxan when it was used as the sole premedicant. The average induction dose in the premedicated cat was 3mg/kg and maintenance dose was 8 mg/kg.

A study was performed to evaluate the clinical efficacy of Alfaxan-CD RTU for cats at a number of veterinary clinics. The formulation used for this study was different from that of the proposed product. A single dose of Alfaxan-CD RTU 2-5mg/kg was sufficient for light anaesthesia and induction, whether or not a premedicant had been used. Incremental doses up to 11mg/kg were shown to be safe and effective for short surgical procedures in non-critical cases.

A study was conducted to evaluate the efficacy of an increased dose of the active substance alfaxalone, and the time to recovery after single or multiple doses of a 10mg/ml solution of alfaxalone solubilised in cyclodextrin. The product Alfaxan-CD was used in this trial which has a similar formulation as Alfaxan. Alfaxan-CD was shown to be safe and effective with a single dose in the range of 3-5mg/kg being sufficient for light anaesthesia or sedation, and intubation for gaseous anaesthesia. Supplemental doses up to 13mg/kg for procedures lasting up to 17 minutes were also safe and did not adversely affect recovery times.

A trial was conducted to evaluate the clinical efficacy in cats of Alfaxan-CD RTU anaesthesia injection, when used at a number of veterinary clinics. The formulation of the product used in this study was different from that of the proposed product. Alfaxan-CD RTU was shown to be safe and effective in the 90 cases studied, either as induction or additionally for maintenance of anaesthesia. A single dose of 2-5mg/kg was sufficient for light anaesthesia and intubation. Longer procedures were possible using doses up to a total of 20mg/kg; through recovery times were correspondingly lengthened.

[1] Abnormal heart rhythms. Can cause the heart to pump less effectively
[2] Absence of breathing
[3] A single dose of drug usually injected into a blood vessel over a short period of time

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 risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.