United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey KT15 3LS

(Reference Member State)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Vetflurane 1000 mg/g Inhalation Vapour, Liquid for Horses, Dogs, Cats, Ornamental Birds, Reptiles, Rats, Mice, Hamsters, Chinchillas, Gerbils, Guinea Pigs and Ferrets, Isoflurane

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/0350/001/DC
Name, strength and pharmaceutical form	Vetflurane 1000 mg/g Inhalation Vapour, Liquid for Horses, Dogs, Cats, Ornamental Birds, Reptiles, Rats, Mice, Hamsters, Chinchillas, Gerbils, Guinea Pigs and Ferrets, Isoflurane
Applicant	Virbac S.A
Active substance(s)	Isoflurane
ATC Vetcode	QN01AB06
Target species	Horses, Dogs, Cats, Ornamental Birds, Reptiles, Rats, Mice, Hamsters, Chinchillas, Gerbils, Guinea Pigs and Ferrets
Indication for use	Induction and maintenance of general anaesthesia

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the mutual recognition procedure	28th March 2018
Date product first authorised in the Reference Member State	16th September 2009
Concerned Member States for original procedure	First Use Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Luxembourg, The Netherlands, Norway, Portugal, Spain, Sweden Repeat Use Czech Republic, Hungary, Norway, Poland, Romania, Slovakia

I. SCIENTIFIC OVERVIEW

This is a generic application for Vetflurane 1000 mg/g Inhalation Vapour, Liquid for Horses, Dogs, Cats, Ornamental Birds, Reptiles, Rats, Mice, Hamsters, Chinchillas, Gerbils, Guinea Pigs and Ferrets. The reference product is IsoFlo 100%w/w Inhalation Vapour, Liquid, authorised for use in the UK since 1996. The species and indications for the generic product are the same as those of the reference product.

The product is indicated for the induction and maintenance of general anaesthesia. In horses, the product may be used in combination with other drugs used in veterinary anaesthetic regimes, but potential interactions must be taken into account. Refer to the Summary of Product Characteristics (SPC) for compatible drugs and possible interactions. Induction of anaesthesia in horses should be preceded by the use of a short-acting barbiturate, followed by concentrations of 3% to 5% isoflurane, allowing the desired depth of anaesthesia in 5 to 10 minutes. Anaesthesia may be maintained using 1.5% to 2.5% isoflurane. In dogs, isoflurane may be used in conjunction with other drugs commonly used in veterinary anaesthetic regimes. Drugs for premedication should be made on an individual patient basis. Compatible drugs and potential interactions are noted in the SPC. Induction is achieved using 5% isoflurane, with or without premedication; maintenance of anaesthesia is achieved with 1.5% to 2.5% isoflurane. In the cat, isoflurane may be used in conjunction with

drugs commonly used in veterinary anaesthetic regimes, with premedication being selected for the individual patient. Refer to the SPC for compatible drugs and possible interactions.

In reptiles, isoflurane is considered the active of choice for many species, with induction occurring at 2% to 4% isoflurane. Maintenance is recommended using 1% to 3% isoflurane. Refer to the SPC for compatible drugs and possible interactions.

For rats, mice, hamsters, chinchillas, gerbils, guinea pigs and ferrets the recommended induction concentration is 2% to 3%, with the maintenance concentration given as 0.25% to 2%. Refer to the SPC for compatible drugs and possible interactions.

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, the consumer of foodstuffs from treated animals 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 100% w/w isoflurane. The container system is an amber type III glass container with a low density polyethylene-lined cap. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the absence of preservative are justified. The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. Satisfactory Good Manufacturing Certificates were obtained for all appropriate sites.

B. Method of Preparation of the Product

No data were required on developmental pharmaceutics, and only minimal development data were required as this is a 100% pure active substance for which formulation details are already in the public domain. The applicant is utilising an active substance which complies with the European Pharmacopoeial monograph, and therefore is of appropriate quality. Comparative impurity profile data for the product and reference product were also not required.

The preparation of the product consists of the filling of 100 ml and 250 ml bottles. Batch size is considered to be the volume held within the holding tank used to fill the bottles. The liquid is filtered, poured into the bottles and the bottles are then sealed

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines, with in-process controls being considered appropriate.

C. Control of Starting Materials

The active substance is an established active substance described in the European 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.

Tests are conducted for appearance of the product, for identification, related substance (impurities), chlorides, fluorides, acidity or alkalinity, non-volatile matter and water content.

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

A declaration was provided that 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

Not applicable.

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 sites have been provided demonstrating compliance with the specification. The finished product tests mirror those for the active substance specification, (see Control of Starting Materials), because the product is 100% isoflurane. This was considered satisfactory. Acceptable batch analysis data were submitted for two batches of product, adhering to the methods specified in the European Pharmacopoeia.

Data from three full-scale production batches were also analysed, and the results were satisfactory.

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.

Three batches of the active substance were stored in 1997. Data were provided for up to three years for each batch and these demonstrated that the product was virtually unchanged. Two batches were stored in 2003. One batch was stored in stainless steel drums and the other in epoxy-lined drums. Both batches of product were subjected to VICH[1] real-time conditions (25°C/60%RH for up to three years, and were tested annually. The product was virtually unchanged. From all studies, a retest period of three years was established.

For the finished product three batches of product were stored in glass vials in both upright and inverted orientation under ambient conditions for up to 24 months, and under VICH accelerated conditions (40oC/75%RH) for up to six months. No change was noted and the product was considered stable under these conditions. A shelf-life of 2 years was approved for the product.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

- Shelf-life of the veterinary medicinal product as packaged for sale is 2 years.
- Do not store above 25°C.
- Protect from direct sunlight and heat.
- Store in tightly closed original container.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13, and bioequivalence with a reference product has been established due to the nature of the product and reference product, results of pharmacological and toxicological tests are not required.

Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the product to users, the environment and consumers.

[1] VICH – International Co-operation on Harmonisation of Technical Requirements for Registration of Veterinary Products.

III.A Safety Testing

User Safety

The applicant provided a user safety assessment in compliance with the relevant guideline, stating that only veterinarians or anaesthetists may administer the product. The major route of exposure is the inhalation route, with the possibility of exposure via the dermal route. The same safety warnings as those of the reference product are included on the product literature for Vetflurane, with the amendment to one phrase so that it reads: 'use cuffed endotracheal intubation when possible for the administration of this product during maintenance of general anaesthesia.'

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 was required. The assessment, carried out in accordance with VICH and CVMP[2] guidelines highlighted the following: the product will be used in both food and non-food species, the product will be administered to small numbers of animals on an individual basis, and that the active substance will not reach soil or water environments. The product will either enter the atmosphere or be trapped within charcoal filters. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

III.B Residues documentation

There is neither acceptable daily intake nor a maximum residues limit for the use of isoflurane in horses. In addition, there is no available data supporting a withdrawal period for milk from mares producing milk for human consumption. The CVMP recommends a withdrawal period of two days for horses treated with isoflurane. The withdrawal period stated for Vetflurane is the same as that used for the reference product.

Withdrawal Periods

For horses, the meat and offal withdrawal period is 2 days. The product should not be used for the treatment of mares producing milk for human consumption.

[2] CVMP – The Committee for Medicinal Products for Veterinary Use.

IV CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13, and bioequivalence with a reference product is established due to the nature of the products, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product. No further data were submitted.

IV.A Pre-Clinical Studies

Pharmacology

As this is a generic application according to Article 13, and bioequivalence with a reference product is established due to the nature of the products, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product. No further data were submitted.

Tolerance in the Target Species of Animals

As this is a generic application according to Article 13, and bioequivalence with a reference product is established due to the nature of the products, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product. No further data were submitted.

IV.B Clinical Studies

Laboratory Trials

As this is a generic application according to Article 13, and bioequivalence with a reference product is established due to the nature of the products, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product. No further data were submitted.

Field Trials

As this is a generic application according to Article 13, and bioequivalence with a reference product is established due to the nature of the products, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product. No further data were submitted.

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

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.

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