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

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

IsoFlo 100% w/w Inhalation Vapour, liquid
(UK, FI, ES, FR, PT, NO, SE, BE, LU, NL, DK, AT, DE, IT))
IsoFlo 100% tekutina k přípravě inhalace parou (CZ)
IsoFlo 100% vodná para na inhaláciu (SK)
IsoFlo (CY, EL)

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0103/001/E/004
Name, strength and pharmaceutical form	IsoFlo 100% w/w Inhalation Vapour, liquid
Applicant	Zoetis UK Limited 5th Floor, 6 St. Andrew Street London EC4A 3AE
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	Mutual Recognition Procedure in accordance with Article 32(2) of Directive 2001/82/EC as amended.
Date of completion of current mutual recognition procedure	26th April 2017
Date product first authorised in the Reference Member State (MRP only)	05 March 1996
Concerned Member States for original procedure	First Use Austria, Belgium, Denmark, Finland, France, Germany, Italy, Luxembourg The Netherlands, Norway, Portugal Spain, Sweden Repeat Use Cyprus, Czech Republic, Greece, Slovakia

I. SCIENTIFIC OVERVIEW

IsoFlo 100% w/w Inhalation Vapour, liquid is authorised for use in horses, dogs, cats, ornamental birds, reptiles, rats, mice, hamsters, chinchillas, gerbils, guinea pigs and ferrets. The product is used for induction and maintenance of general anaesthesia. Each millilitre of product contains 100% isoflurane as an active substance. The product is administered by inhalation using an accurately calibrated vaporiser in an appropriate anaesthetic circuit. The dose is dependent on the species in which the product is being used.

IsoFlo 100% w/w Inhalation Vapour, liquid was submitted as a full application and granted a National MA in the UK in March 1996. The product went through the Mutual Recognition Procedure in May 1998 followed by a first wave Mutual Recognition procedure in December 2000. This application is for a second wave repeat use procedure.

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[1]. 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

[1] SPC - Summary of Product Characteristics

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 the active substance isoflurane.

The product is presented in amber coloured glass bottle in volumes of 100 ml and 250 ml. The bottle has an aluminium roll-on pilfer-proof cap with polyethylene liner and a low-density polyethylene neck collar with wing ("keyed" collar), which is fitted over the cap and bottle neck. The particulars of the containers and controls performed are provided and conform to the current guidelines.

The choice of 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, isoflurane, has no monograph in the European Pharmacopoeia (Ph. Eur). The manufacturer provided details of a testing monograph, and this was considered acceptable. The active substance is manufactured in accordance with the principles of good manufacturing practice.

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.

G. Stability

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. The shelf-life of the veterinary medicinal product as packaged for sale is 5years.

H. Genetically Modified Organisms

Not applicable

J. Other Information

A shelf life of 5 years is justified, subject to the following storage warnings:

- Do not store above 25° C
- Store in the original bottle
- Keep the bottle tightly closed
- Protect from direct sunlight and heat

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant provided data which indicate that isoflurane is a general inhalational anaesthetic of the halogenated ether type. It produces unconsciousness by its action on the CNS[2]. Isoflurane produces relaxation of the skeletal muscle and has no significant analgesic properties.

Isoflurane has high volatility and low solubility (low blood-gas partition coefficient). It is rapidly absorbed, distributed and eliminated. In humans, over 99.5% is exhaled via lungs as unmetabolised isoflurane.

Toxicological Studies

Single dose toxicity:
Single dose toxicity studies were carried out in rats, mice and dogs. The studies were adequately conducted and the results suggested a reasonable margin of safety following single 3 hour exposure by the inhalational route. There were no studies using oral administration.

Repeated dose toxicity:
Repeated dose toxicity studies were carried out in rats, dogs, rhesus monkeys, mice, guinea pigs and rabbits. The repeated administration of isoflurane to several species elicited only minor signs of toxicity such as slight inhibition of food consumption and body weight gain. Fat deposition in the liver and kidney was reported in studies in dogs and rhesus monkeys. There were no pathological changes in these organs in more recent studies in other species employing adequate control groups. A NOEL of 0.13% was established in an adequately conducted 10-week study in rats.

Mutagenicity
No studies indicated that isoflurane produces mutagenic effects.

User Safety

The use of IsoFlo 100% w/w Inhalation Vapour, liquid is not expected to present an undue hazard to the user. The product literature and SPC contain the following safety warnings:

- Do not breathe the vapour. Users should consult their National Authority for advice on Occupational Exposure Standards for isoflurane.
- Operating rooms and recovery areas should be provided with adequate ventilation or scavenging systems to prevent the accumulation of

[2] Central Nervous System

anaesthetic vapour. All scavenging / extraction systems must be adequately maintained.

- Pregnant and breast- feeding women should not have any contact with the product and should avoid operating rooms and animal recovery areas. Avoid using masking procedures for prolonged induction and maintenance of general anaesthesia.
- Use cuffed endotracheal intubation when possible for the administration of Isoflo during maintenance of general anaesthesia.
- To protect the environment, it is considered good practice to use charcoal filters with scavenging equipment.
- Care should be taken when dispensing isoflurane, with any spillage removed immediately using an inert and absorbent material e.g. sawdust. Wash any splashes from skin and eyes, and avoid contact with the mouth. If severe accidental exposure occurs remove the operator from the source of exposure, seek urgent medical assistance and show this label.
- Halogenated anaesthetic agents may induce liver damage. In case of isoflurane this is an idiosyncratic response very rarely seen after repeated exposure.
- *Advice to Doctors:* Ensure a patent airway and give symptomatic and supportive treatment. Note that adrenaline and catecholamines may cause cardiac dysrhythmias.

Ecotoxicity

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

Residue Studies

The data provided indicated that the product should not pose a risk for the consumer when used as recommended in the SPC.

Withdrawal Periods

Based on the data provided, a withdrawal period of 2 days for meat in horses is justified.

IV CLINICAL ASSESSMENT (EFFICACY)

Pharmacology

Pharmacodynamic:
Isoflurane produces unconsciousness by its action on the central nervous system.
Like other inhalation anaesthetics of this type, isoflurane depresses the respiratory and cardiovascular systems. Isoflurane is absorbed on inhalation

and is rapidly distributed via the bloodstream to other tissues, including the brain. Its blood/gas partition coefficient at 37° C is 1.4. The absorption and distribution of Isoflurane and the elimination of non-metabolised isoflurane by the lungs are all rapid, with the clinical consequences of rapid induction and recovery and easy and rapid control of the depth of anaesthesia.

Pharmacokinetics
Metabolism of isoflurane is minimal (about 0.2%, mainly to inorganic fluoride) and almost all of the administered isoflurane is excreted unchanged by the lungs.

Tolerance in the Target Species of Animals

A review of published data was submitted in support of this section. In general, the published literature demonstrated the wide use of isoflurane in many species with no specific safety problems. The low solubility of isoflurane makes it preferable to other agents because a relative overdose can be rapidly recovered from the patient by artificial ventilation.

IV.B Clinical Studies

All data submitted supported the claims in the SPC for this product.

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)