ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
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Surrey KT15 3LS

(Reference Member State)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Iso-Vet 1000 mg/g Inhalation Vapour, liquid (Austria, Belgium, France, Germany, Greece, Ireland Italy, The Netherlands, Poland, Romania, United Kingdom)
IsoVet 1000 mg/g Inhalation Vapour, liquid (Spain, Portugal)
Altane vet 1000 mg/g Inhalation Vapour, liquid (Denmark, Sweden, Finland, Iceland)

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0300/001/DC
Name, strength and pharmaceutical form	Iso-Vet, Isoflurane 1000 mg/g Inhalation Vapour, liquid (all CMS except Spain) Isoflurane, Isovet 1000mg/g Inhalation Vapour, liquid (Spain only)
Applicant	Piramal Critical Care Limited Suite 4, Ground Floor Heathrow Boulevard - East Wing 280 Bath Road West Drayton UB7 0DQ United Kingdom
Active substance(s)	Isoflurane
ATC Vetcode	QN01AB06
Target species	Horses, dogs, cats, ornamental birds, reptiles, rats, mice, hamsters, chinchillas, gerbils, guinea pigs, ferrets and piglets.
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 original decentralised procedure	12/08/2009
Date product first authorised in the Reference Member State (MRP only)	NA
Concerned Member States for original procedure	Germany, The Netherlands, Portugal, Spain CMSs added during Repeat Use procedure Austria, Belgium, Denmark, Finland, France, Greece, Iceland, Ireland, Italy, Poland, Portugal, Romania, Sweden

1. SCIENTIFIC OVERVIEW

This is an application for a generic product made in accordance with Article 13 (1) of Directive 2001/82/EC, as amended. The reference product is Isoflo Inhalation Vapour, Liquid.

Iso-Vet, Isoflurane 1000 mg/g Inhalation Vapour, Liquid, is intended for the induction and maintenance of general anaesthesia in a variety of target species. The target species are as follows: horses, dogs, cats, ornamental fowl, reptiles, rats, mice, hamsters, chinchillas, gerbils, guinea pigs and ferrets. The product is not suitable for rabbits.

Isoflurane is to be administered using an accurately calibrated vaporiser in an appropriate anaesthetic circuit. The product may be administered in oxygen or oxygen/nitrous oxide mixtures. Data provided in the SPC[1] on the minimal alveolar concentration in oxygen (MAC), and/or the effective dose (ED_{50}) for each species, are provided as a guide or starting point only. Isoflurane may be used in conjunction with other drugs commonly used in veterinary anaesthesia, some information for which is provided in the SPC. There is usually a rapid and smooth recovery after the use of isoflurane anaesthesia.

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

[1] SPC – Summary of Product Characteristics.

shown that the product can be safely used in the target species, and the 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% isoflurane and there are no excipients.

The containers for the product are either 100 ml or 250 ml type III, amber glass bottles. The closures for the bottles are black, phenolic/urea screw-fit caps with an internal low density polyethylene cone liner. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and 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.

B. Method of Preparation of the Product

The product consists solely of 100% isoflurane, and therefore manufacturing requirements consist only of the filling of 100 ml and 250 ml bottles. The bulk product is placed in stainless steel drums, and the volume required is then moved to a bulk holding tank via a porous sintered steel filter. Isoflurane is then poured into the glass bottles in which the product is to be sold, the quantity being determined gravimetrically.

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, and the product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C. Control of Starting Materials

The active substance is isoflurane, an established active substance described in the European 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. There are no excipients.

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

No substances within the scope of the TSE Guideline are 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

Tests on the final product include observation of solubility, identification by infrared absorption, measurement of acidity or alkalinity and the presence of chlorides or fluorides. Appropriate tests are performed on the two starting materials, 2,2,2-trifluoroethanol and chlorodifluoromethane, and an analysis of any residues or impurities is also performed. Each bottle of finished product is inspected visually before being packaged into the appropriate carton, for which labelling and coding details are checked. 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.

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 active substance were stored in stainless steel drums and tested at 30°C/65% RH (real time) and 40°C/75% RH (accelerated test). Results were satisfactory. A retest period of 24 months was considered acceptable for the active substance.

A shelf-life of five years is acceptable for this product, based on the applicant's knowledge of the shelf-life of the reference product. Due to the volatile nature of the product, storage warnings are as follows: do not store above 25°C, protect from direct sunlight and direct heat, store in tightly closed original container.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Data were supplied which justified a five-year shelf life of the product as packaged for sale, with a recommendation that storage is below 25°C, the product is protected from sunlight and heat, and stored in the tightly closed original container. The shelf-life of the product as packaged for sale is 5 years.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13 (1), and bioequivalence with the reference product can be assumed because of the nature of the product, results of pharmacological and toxicological tests and clinical trials are not required.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the following safety precautions should be adhered to:

- 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 anaesthetic vapour.
- All scavenging/ extraction systems must be adequately maintained.
- Pregnant and/or breast- feeding women should avoid exposure to the product and should avoid operating rooms and recovery areas.
- Avoid using masking procedures for prolonged induction and maintenance of general anaesthesia. Use cuffed endotracheal intubation when possible for the administration of isoflurane 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.

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

Ecotoxicity

The applicant provided a Phase I 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. In order to protect the environment, charcoal filters should be used in scavenging equipment within the operating room.

III.B Residues documentation

Residue Studies

No residue depletion studies were conducted because the application was made in accordance with Article 13 (1) of Directive 2001/82/EC, as amended, under the specified conditions for a generic application. No data was provided in this section.

Withdrawal Periods

Based on the bioequivalence with the reference product, a withdrawal period of 2 days for meat from horses is justified. Do not use in mares producing milk for human consumption.

IV CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13 (1) of Directive, 2001/82/EC, as amended and bioequivalence with the reference product can be assumed because of the nature of the product, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product, Isoflo Inhalation Vapour, Liquid.

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

As this is a generic application according to Article 13 (1), of Directive, 2001/82/EC, as amended and bioequivalence with a reference product can be assumed because of the nature of the product, no data are required for this section.

IV.B Clinical Studies

As this is a generic application according to Article 13 (1), of Directive, 2001/82/EC, as amended and bioequivalence with a reference product can be assumed because of the nature of the product, no data are required for this section.

Laboratory Trials

As this is a generic application according to Article 13 (1), of Directive, 2001/82/EC, as amended and bioequivalence with a reference product can be assumed because of the nature of the product, no data are required for this section.

Field Trials

As this is a generic application according to Article 13 (1), of Directive, 2001/82/EC, as amended and bioequivalence with a reference product can be assumed because of the nature of the product, no data are required for this section.

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.

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