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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)

NL/V/0246/001 (former: UK/V/0300/001/DC)

Created by UK

18 December 2017 RMS change from UK to NL

Updated: March 2022

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0246/001 (former: UK/V/0300/001)
Name, strength and pharmaceutical form	Iso-Vet 1000 mg/g Inhalation Vapour, liquid (Austria, Belgium, Germany, France, Greece, Ireland, Italy, Poland, Romania, United Kingdom (Northern Ireland)) IsoVet 1000 mg/g Inhalation Vapour, liquid (Spain & Portugal) Attane vet 1000 mg/g Inhalation Vapour, liquid (Denmark, Sweden, Finland & Iceland)
Applicant	Piramal Critical Care B.V. Rouboslaan 32 (Ground Floor), 2252 TR Voorschoten The Nederlands
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 (up to 7 days of age)
Indication for use	Horses, dogs, cats, ornamental birds, reptiles, rats, mice, hamsters, chinchillas, gerbils, guinea pigs and ferrets: Induction and maintenance of general anaesthesia Piglets (up to 7 days of age): For general anaesthesia during the castration of male piglets in combination with the preoperative parenteral administration of a suitable analgesic to relieve postoperative pain.

Iso-Vet 1000 mg/g Inhalation Vapour, liquid	NL/V/0246/001
Piramal Critical Care B.V.	DCP
	Publicly available assessment report

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, United Kingdom (Northern Ireland). 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. In piglets (up to 7 days of age) Iso-vet, Isoflurane 1000 mg/g Inhalation Vapour, Liquid, is intended for general anaesthesia during the castration of male piglets in combination with the preoperative parenteral administration of a suitable analgesic to relieve postoperative pain. 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.

[1] SPC – Summary of Product Characteristics.

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, 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/polypropylene 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 30ºC/65% RH (real time) and 40ºC/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 25ºC, 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 25ºC, 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:

Isoflurane induces anaesthesia in humans. Moreover, it may induce liver damage and also allergic reactions to isoflurane have been reported. Fatigue, headache, or reduced reaction times have been reported at exposures below therapeutic doses. Splashes to the eye may induce irritation.

Do not breathe the vapour. Wash any splashes from skin and eyes, and avoid contact with the mouth.

Care should be taken when dispensing isoflurane, with any spillage removed immediately using an inert and absorbent material e.g. sawdust.

Contaminated work clothing should be taken off and washed before reuse.

Operating rooms and recovery areas should be provided with adequate ventilation or scavenging systems to prevent the accumulation of anaesthetic vapour. 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.

In the event of isoflurane odour or adverse health effects such as dizziness etc remove from the source of exposure and go to fresh air. In case of severe accidental exposure seek urgent medical assistance and show this label.

Isoflurane passes the placenta and transfers from maternal to foetal blood. Adverse effects on foetuses and pregnant animals were observed in laboratory animals. Pregnant and/or breast- feeding women should not have any contact with the product and should avoid operating rooms and animal recovery areas.

Adverse effects on male fertility cannot be excluded. In male rats, effects on fertility parameters were observed after repeated exposure at higher concentrations. Prevent inhalation exposure to high concentrations by carefully following the instructions in the product information.

Piglets (up to 7 days of age)

In order to ensure that the safety of the workplace is maintained, castration may only be carried out using an appropriate inhalation device equipped with scavenging double masks.

The exposure of the user should be kept as low as possible. Operating theatres and recovery areas should be equipped with adequate ventilation to prevent accumulation of isoflurane vapours in the air breathed. In the case of underfloor ventilation, artificial ventilation must be set.

When the anaesthetic gas is used in a pig holding, a suitable isoflurane filling device should be used. Isoflurane tanks should preferably be filled outdoors, but at least in very well- ventilated rooms outside the rooms where animals are kept, with as few staff in the room as possible. It is recommended that the filling of isoflurane is monitored by additional personnel not involved in the filling process in case of an accidental exposure event.

Vaporizers should be switched off when not in use. It is advisable to have an isoflurane container with a capacity adapted to the amount needed for a whole day, so that the container does not need to be filled during anaesthesia.

It must be ensured that the mask used seals tightly for each individual piglet in order to avoid additional exposure of the workplace. Free escape from an unoccupied anaesthesia mask (no piglets in anaesthesia mask) must be prevented.

To the physician: Ensure a patient airway is clear and give symptomatic and supportive treatment. Note that adrenaline and catecholamines may cause cardiac arrhythmias.'

Other Precautions: Isoflurane is a gas with a global-warming potential and ozone depletion potential; thus it is good practice to use charcoal filters with scavenging equipment, rather than to discharge the gas into the air.

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.

During the line extension to add target species piglets (up to 7 days of age) no residue depletion studies were conducted. For isoflurane, there is no MRL required in piglets up to 7 days of age. A safety margin of 2 days has been taken in to account and satisfactorily justified.

Withdrawal Periods

Based on the bioequivalence with the reference product, a withdrawal period of 2 days for meat from horses and piglets (up to 7 days of age) 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 for the target species horses, dogs, cats, ornamental fowl, reptiles, rats, mice, hamsters, chinchillas, gerbils, guinea pigs and ferrets. The efficacy claims for this product are equivalent to those of the reference product, Isoflo Inhalation Vapour, Liquid. For the target species piglets (up to 7 days of age) bibliographical data on the clinical use of isoflurane for anaesthesia during castration has been provided.

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.

The applicant has provided bibliographical data with general knowledge on isoflurane tolerance in pigs, which supports the safe use in piglets. The adverse

events section in the SPC and package leaflet provide information on potential adverse events.

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.

The applicant provided bibliographical data on clinical application (field use) of isoflurane for anaesthesia during castration of piglets up to 7 days of age. Most of the evidence available from public available literature shows that isoflurane is efficacious in general anaesthesia of piglets under 8 days of age for castration. It can be concluded that the induction is quick, and recovery smooth and most of the time uneventful. From the cited literature it can be concluded that administration of additional analgesics is strongly recommended. The administration of additional analgesics not only leads to a sufficient depth and width of anaesthesia with unconsciousness, analgesia and muscle relaxation, but also to fewer defensive movements and thus low-stress or stress-free castration and a short recovery phase. In addition, the analgesic administered in advance reduces the postoperative castration pain. These aspects are sufficiently covered in the SPC.

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 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.

Summary of change (procedure number)	**Section updated**	**Approval date**
To change the name of the quality control testing site (UK/V/0300/001/IA/001).	N/A	21 December 2009
To change the name of the active substance manufacturer and finished product manufacturer (UK/V/300/001/IA/002).	N/A	21 December 2009
To change the name and address of contract quality control testing site (UK/V/0300/001/IA/003).	N/A	21 December 2009
Replacement of a manufacturer responsible for batch release, not including batch control/testing (UK/V/0300/001/IA/004)	Package leaflet	21 December 2009
Repeat Use procedure. UK as RMS CMSs added during Repeat Use procedure: Austria, Belgium, Denmark, Finland, France, Greece, Iceland, Ireland, Italy, Poland, Portugal, Romania, Sweden (UK/V/0300/001/E/001)	Module 3	24 November 2010
Removal of the impurities from the active substance specification. Removal of the impurities from the finished product specification. Change in batch size from 3500-4200 kg to 6300 – 7700 kg. Change in the manufacturing process of the active substance. (UK/V/0300/001/IB/006/G)	N/A	3 June 2011

To change the SPC, labeling and package leaflet according to another similar product (UK/V/0300/001/II/005).	SPC	10 August 2011
Change of the Marketing Authorisation Holder and batch release site. Changes to the batch release arrangements and quality control testing of the finished product. (UK/V/0300/001/IA/007/G)	SPC, module 1	12 January 2012
Tightening of in-process fill limit during the manufacture of the finished product. Tightening of specification limits of finished product (UK/V/0300/001/IA/008/G)	N/A	12 April 2013
Change in the name of manufacturer of finished product. Change in the name of manufacturer of the drug substance. (UK/V/0300/IA/009/G)	N/A	25 April 2013
Change to the back-up QPPV. Minor changes to the DDPS. (UK/V/0300/001/IA/010/G)	N/A	1 August 2014
Renewal (UK/V/0300/001/R/001)	N/A	8 August 2014
To increase the batch size of the finished product, from 1500 kg to 3000 kg (UK/V/0300/001/IA/011)	N/A	13 November 2014
Change in the address of the manufacturer of the active substance. Change in the address of the manufacturer of the finished product. (UK/V/0300/IA/012/G)	N/A	24 February 2016
Change in the name of a manufacturer of the finished product (UK/V/0300/001/IA/013)	N/A	15 March 2017
Change of MAH from Piramal Healthcare UK Limited to Piramal Critical Care Limited (national variations).	Module 1, SPC, Labelling, Package leaflet	August–October 2017
Change in the RMS from UK to NL. Procedure number change from UK/V/0300/001 to NL/V/0246/001.	Module 1	18 December 2017
Addition of an alternative cap for the primary packaging (NL/V/0246/001/IA/015)	N/A	8 September 2018

Change in the address of an active substance manufacturer. Change in the address of a manufacturer of the finished product. Replacement of a site where batch control/testing takes place. (NL/V/0246/IA/016/G)	N/A	8 September 2018
Changes in the SPC, Labelling or Package Leaflet of a generic product following assessment of the same change for the reference product, for which no new additional data is required (NL/V/0246/001/IB/014).	SPC, labelling and package leaflet	21 October 2018
Introduction of a new DDPS which has been assessed by the relevant NCA/EMA for another product of the same MAH (NL/V/0246/001/IB/017)		12 December 2018
Addition of a manufacturer responsible for batch release of the finished product, not including batch control (NL/V/0246/001/IA/018)	Package leaflet	9 January 2019
Transfer of MAH from Piramal Critical Care Limited to Piramal Critical Care B.V. (national variations)	Modules 1 and 3, SPC, Labelling, Package leaflet	March 2019
Replacement of a manufacturer responsible for batch release of the finished product, not including batch control (NL/V/0246/001/IA/019).	Package leaflet	27 March 2019
Replacement of a site where batch control/testing takes place (NL/V/0246/001/IA/020).	N/A	10 May 2019
Change in the qualitative and quantitative composition of immediate packaging of the finished product (NL/V/0246/001/IB/022).	N/A	17 August 2019
Introduction of a new DDPS which has been assessed by the relevant NCA/EMA for another product of the same MAH (NL/V/0246/001/IB/021).	N/A	11 September 2019
Update of the dossier to comply with an updated general monograph of the Ph. Eur for the finished product. Minor changes to an approved test procedure. (NL/V/0246/IB/023/G)	N/A	21 September 2019
Several changes to the control of the active substance (NL/V/0246/001/II/024).	N/A	14 May 2020
Changes to a test procedure for a starting material used in the manufacturing of the active substance	N/A	1 August 2020

(NL/V/0246/001/IB/026)		
Addition of an alternate supplier for one of the starting materials of the active substances (NL/V/0246/001/IB/025)	N/A	3 September 2020
Change in packaging material not in contact with the finished product formulation (NL/V/0246/001/IA/027/G)	Module II, SPC	3 September 2020
Change in the batch size of the finished product up to 10-fold compared to the originally approved batch size (NL/V/0246/001/IA/028)	N/A	15 October 2020
Change in the QPPV Other change to the DDPS that do not affect the operations of the pharmacovigilance system (NL/V/0246/001/IA/029/G)	N/A	30 December 2020
Change in the name of the manufacturer of the finished product and of the manufacturer of the active substance. (NL/V/0246/001/IA/030/G)	N/A	21 February 2021
Change in deputy QPPV and contact details (NL/V/0246/001/IA/031)	N/A	31 March 2021
Deletion of manufacturing sites responsible for batch release (NL/V/0246/001/IA/032)	Package leaflet	31 July 2021
Line extension (addition of target species piglets up to 7 days of age) (NL/V/0246/001/DX/001)	Module I and 3 SPC, labelling, package leaflet	20 October 2021
Change in a specification limit, addition of a new specification parameter, replacement of a supplier for caps. (NL/V/0246/001/IB/033/G)	N/A	5 January 2022
Minor change in the manufacturing process of the active substance and addition of a new specification. (NL/V/0246/001/IB/034/G)	N/A	9 February 2022