College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
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The Netherlands

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Isothesia 1000 mg/g Inhalation Vapour, Liquid (AT, BE, CZ, DE, DK, EL, NL, FI, FR, IE, IT, PL, RO, SE)

Isofane 1000 mg/g Inhalation Vapour Liquid (ES)

NL/V/0291/001/DC

Created: March 2022
Updated: January 2024

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0291/001/DC
Name, strength and pharmaceutical form	Isothesia, 1000 mg/g inhalation vapour, liquid
Applicant	Piramal Critical Care B.V. Rouboslaan 32 (ground floor), 2252 TR Voorschoten The Netherlands
Active substance(s)	Isoflurane
ATC Vet code	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.

Isothesia	NL/V/0291/001/DC
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 Veterinary Medicines Agencies website (http://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	25 September 2019
Concerned Member States for original procedure	AT, BE, DE, DK, EL, ES, FI, FR, IE, IT, PL, RO, SE.
Concerned Member States for subsequent recognition procedure (SRP)	CZ

I. SCIENTIFIC OVERVIEW

Isothesia is a generic product; the reference medicinal product is ISOFLO 100% w/w vloeistof voor inhalatiedamp (REG NL 9132, Procedure: ES/V/0325/001) by Zoetis B.V., which was registered in the Netherlands on the 10th of August 1998. During the original authorisation procedure, completed on 25 September 2019, Isothesia was a duplicate application to Iso-vet 1000 mg/g Inhalation Vapour, Liquid (procedure NL/V/0246/001). The first wave SRP was completed on 2 January 2024.

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 risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

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 or 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 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.

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

D. Control on intermediate products

There are no intermediate products.

E. 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.

F. 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 25 ºC, protect from direct sunlight and direct heat, store in tightly closed original container in order to protect from moisture.

G. Other Information

None.

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.

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.

Environmental Risk Assessment

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.

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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 and offal 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.

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.

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 Heads of Veterinary Medicines Agencies website (www.HMA.eu).

This section 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	**Section updated**	**Approval date**
NL/V/0291/IA/001/G 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.	N/A	7 February 2020
NL/V/0291/001/II/002 Multiple changes in control of active substance	N/A	18 August 2020
NL/V/0291/001/IB/003 Addition of an alternate supplier for one of the starting materials of the active substances	N/A	14 October 2020
NL/V/0291/001/IB/004 Change in test procedure for starting material used in the manufacturing process of the active substance.	N/A	14 October 2020
NL/V/0291/001/IA/005 Change in the batch size of the finished product up to 10-fold compared to the originally approved batch size	N/A	15 October 2020
NL/V/0291/001/IB/006 Change in immediate packaging of the finished product	Module II, SPC	16 December 2020
NL/V/0291/IA/007/G Change in the QPPV Other change to the DDPS that do not affect the operations of the pharmacovigilance system	N/A	30 December 2020
NL/V/0291/IA/008/G Change in the name of the manufacturer of the finished product and of the manufacturer of the active substance.	N/A	7 February 2021
NL/V/0291/001/IA/009 Deletion of manufacturing sites responsible for batch release and batch control testing	Package leaflet	5 March 2021
NL/V/0291/001/IA/010 Change in deputy QPPV and contact details	N/A	24 March 2021
NL/V/0291/IB/011/G Change in a specification limit, addition of a new specification parameter, replacement of a supplier for caps.	N/A	23 November 2021
NL/V/0291/IB/012/G Minor change in the manufacturing process of the active substance Change to in-process tests or limits applied during the manufacture of the active substance; other variation	N/A	15 April 2022

NL/V/0291/A/013 Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate	N/A	11 October 2023
NL/V/0291/A/014 Change in test procedure for the finished product Other changes to a test procedure (including replacement or addition)	N/A	11 October 2023