

IPAR



**Publicly Available Assessment Report for a
Veterinary Medicinal Product**

Isocare 1000 mg/g Inhalation Vapour, Liquid

PRODUCT SUMMARY

EU Procedure Number	IE/V/0458/001 (formerly UK/V/0589/001)
Name, Strength, Pharmaceutical Form	Isocare 1000 mg/g Inhalation Vapour, Liquid
Active Substances(s)	Isoflurane
Applicant	Ecuphar NV Legweg 157-I 8020 Oostkamp Belgium
Legal Basis of Application	Generic application (Article 13(1) of Directive No 2001/82/EC)
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.
ATC Code	QN01AB06
Date of completion of the original decentralised procedure	28 April 2016 (UK) 16 August 2016 (IE)
Date of completion of current MRP procedure	20 September 2017
Concerned Member States for original procedure	<u>First Use</u> Austria, Belgium, Denmark, Finland, France Germany, Hungary, Ireland (now RMS), Iceland, Italy, Luxembourg, The Netherlands, Norway, Portugal, Spain, Sweden <u>Repeat Use</u> Croatia, Cyprus, Estonia, Greece, Poland, Romania, Slovakia and Slovenia UK added via RMS change

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.

The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

I. SCIENTIFIC OVERVIEW

This was a generic application submitted in accordance with Article 13 (1) of Directive 2001/82/EC (as amended). The marketing authorisation was granted on the basis of essential similarity to the reference product. The reference product is IsoFlo 100% w/w Inhalation Vapour, Liquid, marketed in the UK since March 1996. The product was eligible for a biowaiver from *in vivo* bioequivalence studies in accordance with 7.1(f) of the Guideline on the conduct of bioequivalence for veterinary medicinal products (EMA/CVMP/016/00-Rev.2), which states:

'Studies to compare the rate and extent of absorption between two formulations or products containing identical active substances are generally not required if both products fulfil one or more of the following conditions:

f) The product is intended to be a gas for inhalation at the time of administration

The indication is for the induction and maintenance of general anaesthesia, for horses, dogs, cats, ornamental birds, reptiles, rats, mice, hamsters, chinchillas, gerbils, guinea pigs and ferrets.

The product should be administered using an accurately calibrated vaporiser, in an appropriate anaesthetic circuit, since levels of anaesthesia may be altered rapidly and easily. Isoflurane is administered in oxygen or oxygen/nitrous oxide mixtures. The minimal alveolar concentration (MAC) in oxygen or effective dose (ED₅₀) values provided in the Summary of Product

Characteristics (SPC) are to be used as a guide or starting point only. The SPC provides further specific information on use and warnings related to the product. Refer to the SPC for details on premedication, induction of anaesthesia, dose, contraindications and interactions with other active substances. Recovery from anaesthesia with isoflurane is usually smooth and rapid.

Horse

In horses, the MAC for isoflurane is approximately 1.31%. Anaesthesia is maintained using 1.5% to 2.5% isoflurane. It is not normally practicable to induce anaesthesia in horses using isoflurane.

Dog

The MAC for isoflurane in the dog is approximately 1.28%. Anaesthesia may be maintained using 1.5% to 2.5 % isoflurane.

Cat

The MAC for isoflurane for the cat is approximately 1.63%. Anaesthesia should be maintained using 1.5% to 3%.

Ornamental birds

Few MAC/ED₅₀ values have been recorded. Examples are 1.34% for the Sandhill crane, 1.45% for the racing pigeon, (reduced to 0.89% by the administration of midazolam), and 1.44% for cockatoos, reduced to 1.08% by the administration of butorphanol analgesic.

The use of isoflurane anaesthesia has been reported for many species, from small birds such as zebra finches, to large birds such as vultures, eagles and swans.

Reptiles

The use of isoflurane anaesthesia has been reported for many species. The ED₅₀ was determined in the desert iguana to be 3.14% at 35°C and 2.83% at 20°C. No specific publications on reptiles show a review of compatibilities or interactions of other drugs with isoflurane anaesthesia. Maintenance of anaesthesia is given as between 1% to 3% as a useful concentration.

Rats, mice, hamsters, chinchillas, gerbils, guinea pigs and ferrets

The MAC for mice has been cited as 1.34%, and for rats as 1.38%, 1.46% and 2.4%. The maintenance concentration of isoflurane in these species is recommended as being between 0.25% and 2%.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto the market. It has been shown that the product can be safely used in the target species, any reactions observed are indicated in the SPC. The product is safe for the user, the consumer of foodstuffs from treated animals (horses), and for the environment, when used as recommended. The product is not to be used in mares producing milk for human consumption. Suitable warnings and precautions are indicated in the SPC. The efficacy [1] 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.

[1] Efficacy – The production of a desired or intended result.

II. QUALITY ASPECTS

II.A. Composition

The product contains 1000 mg isoflurane and no excipients. The container/closure system consists of amber coloured glass bottle (Type III) containing 250ml isoflurane. 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 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.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of filling the isoflurane into bottles using suitable filtration. Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.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. An acceptable certificate of suitability was provided. The product is presented in line with additional specifications for refractive index and limits for isoflurane content and limits for boiling point and low boiling point impurities.

II.C.4. Substances of Biological Origin

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product. European Medicines Agency Tables were provided which complied with the Note for Guidance for Minimising the Risk of Transmitting Animals Spongiform Encephalopathy Agents via Veterinary Medicinal Products (EMA/410/01 rev 3).

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable. The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

II.E. 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 site have been provided demonstrating compliance with the specification. Control tests on the finished product include those for appearance, identification of the active substance, refractive index, boiling point, pH, relevant ion content, residue and water content and the presence of impurities.

II.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. The re-test period is 5 years. Stability studies were provided for 3 batches of finished product. Samples were stored in 250 ml containers under VICH [1] conditions for 6 months at 40°C/75% RH; upright and inverted. Samples were also stored for 18 months at 25°C/60% RH upright and inverted. Studies were also performed on samples stored at 25°C/60% RH for 60 months.

G. Other Information

Isoflurane has been reported to interact with dry carbon dioxide absorbents to form carbon monoxide. In order to minimise the risk of formation of carbon monoxide in rebreathing circuits and the possibility of elevated carboxyhaemoglobin levels, carbon dioxide absorbents should not be allowed to dry out.

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.

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

[1] VICH - International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13 (1), and bioequivalence with a reference product has been established by means of essential similarity, results toxicological and pharmacological studies 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.

III.A Safety Documentation

User Safety

A user risk assessment was provided in compliance with the relevant guideline. These warnings are similar to those of the reference product, with some additions. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

- 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 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 the veterinary medicinal product 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.

Environmental Safety

Phase I:

A Phase I ERA (environmental risk assessment) was presented. The product will be used to treat a small number of animals, and as such environmental exposure will be low. A Phase II ERA was not required.

III.B.2 Residues documentation

Residue Studies

No residue depletion studies were conducted because the proposed product and reference product were shown as being essentially similar. A CVMP [1] Summary Report (EMEA/MRL/222/97-FINAL, May 1997), noted that a two day withdrawal period could be established for the use of isoflurane in horses. The SPC additionally carries a warning not to use the product in mares producing milk for human consumption.

MRLs

The CVMP considered that there is no need to establish an MRL[2] for isoflurane.

Withdrawal Periods

Based on the data provided, the following withdrawal periods are justified. Horses:

Meat and offal: 2 days

Milk: Not authorised for use in mares producing milk for human consumption.

[1] CVMP – The Committee for Veterinary Medicinal Products

[2] MRL – maximum residue limit.

IV. CLINICAL ASSESSMENT

As this is a generic application according to Article 13 (1), and essential similarity with a reference product has been established, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

Tolerance in the Target Species

As this is a generic application according to Article 13 (1), and essential similarity with a reference product has been established, tolerance studies are not required. The safety claims for this product are equivalent to those of the reference 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 of the product(s) is favourable.