IPAR

Public Assessment Report for a Medicinal Product for Human Use

Scientific discussion

Sevoflurane 100% inhalation vapour, liquid
Sevoflurane
PA0688/036/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. 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 medicinal product for marketing in Ireland.

CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Sevoflurane 100%, inhalation vapour, liquid, sevoflurane, 100% inhalation vapour liquid, from Chanelle Medical on <DATE of authorisation>for induction and maintenance of general anaesthesia in adult and paediatric patients. Use of sevoflurane in dental anaesthesia should be restricted to hospitals or day care units only.

This application for a national marketing authorisation was submitted in accordance with Article 10(1) of Directive 2001/83/EC and is referred to as a "generic" application.

This product is a prescription only medicinal product to be promoted only to the medical profession.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie.

Name of the product	Sevoflurane 100% inhalation vapour, liquid
Name(s) of the active substance(s) (INN)	SEVOFLURANE
Pharmacotherapeutic classification (ATC code)	N01AB08
Pharmaceutical form and strength(s)	100% Inhalation Vapour Liquid
Marketing Authorisation Number(s) in Ireland (PA)	PA 688/36/1
Marketing Authorisation Holder	Chanelle Medical

II QUALITY ASPECTS

II.1. Introduction

This application is for Sevoflurane 100% inhalation vapour, liquid.

II.2 Drug substance

The active substance is sevoflurane, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The drug product consists of Sevoflurane Ph. Eur. 250 ml, filled into amber glass bottles. There are no excipients.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/Ancillary Substances)

The product consists entirely of sevoflurane and contains no other substances.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for Sevoflurane Ph. Eur. with the addition of a control on the minimum fill volume per bottle. The tests and control limits are considered appropriate for this type of product.

The analytical methods are described in sufficient detail. They are either described in the European Pharmacopoeia or are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided and demonstrate the ability of the manufacturer to produce a finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with relevant pharmaceutical and toxicological requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Sevoflurane 100 % inhalation vapour, liquid.

III NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Sevorane 100% v/v Inhalation Gas on the Irish market by AbbVie Limited. No new pre-clinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

Adequate justification has been provided for the absence of specific studies in the environmental risk assessment. This product is intended for generic substitution and no increase in environmental exposure is anticipated.

III.6 Discussion on the non-clinical aspects

This active substance is a generic formulation of Sevorane 100% v/v Inhalation Gas on the Irish market by AbbVie Limited. No new pre-clinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

IV CLINICAL ASPECTS

IV.1 Introduction

This is a generic application submitted under article 10(1) of Directive 2001/83/EC.

Sevoflurane is a well-known active substance with established efficacy and tolerability.

The content of the SmPC approved during this national procedure is in accordance with that accepted for the reference product Sevorane 100% v/v Inhalation Gas marketed in Ireland by AbbVie Limited.

As per current bioequivalence guidelines (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), no bioequivalence study is submitted or required as the product in question is a gas for inhalation.

IV.2 Pharmacokinetics

The low solubility of sevoflurane in blood would suggest that alveolar concentrations should rapidly increase upon induction and rapidly decrease upon cessation of the inhaled agent. This was confirmed in a clinical study.
In humans, < 5% of sevoflurane absorbed is metabolised, in the liver, to hexafluoroisopropanol (HFIP) with release of inorganic fluoride and carbon dioxide (or a one carbon fragment). Once formed, HFIP is rapidly conjugated with glucuronic acid and excreted in the urine.
The rapid and extensive pulmonary elimination of sevoflurane minimises the amount of anaesthetic available for metabolism. The metabolism of sevoflurane is not inducible by barbiturates.

IV.3 Pharmacodynamics

Changes in the clinical effects of sevoflurane rapidly follow changes in the inspired concentration.
Recovery of cognitive function and motor co-ordination have been evaluated compared to the reference medicine using a meta-analysis of data generated in clinical trials. Patients administered sevoflurane reached criteria required for discharge from the recovery room significantly sooner than those administered the reference medicine.

Cardiovascular Effects
As with all other inhalation agents, sevoflurane depresses cardiovascular function in a dose related fashion.

Nervous System Effects
No evidence of seizure was observed during the clinical development programme. Sevoflurane does not have any stimulating effect on the sympathetic nervous system.

IV.4 Clinical Efficacy

The clinical efficacy of sevoflurane is well established. No additional efficacy clinical studies to demonstrate efficacy have been included in the application. This is appropriate for this type of application.

IV.5 Clinical Safety

The clinical safety of sevoflurane is well established. No additional safety clinical studies to demonstrate safety have been included in the application. This is appropriate for this type of application.

Summary of the Pharmacovigilance System
The marketing authorisation holder (MAH) submitted a summary of the Pharmacovigilance System, including confirmation of the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

Risk Management Plan (usual pharmacovigilance requirements +/- additional requirements)

The applicant should follow the PSUR submission cycle as adopted in the final version of the European Union Reference Dates (EURD) list.

IV.6 Discussion on the clinical aspects

As this is a generic application under Article 10(1) of Directive 2001/83/EC, additional non-clinical and clinical studies to demonstrate efficacy and safety are not required.

As per current bioequivalence guidelines (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), no bioequivalence study is submitted or required as the product in question is a gas for inhalation.

The benefit/risk profile of the product is considered to be positive.

V OVERALL CONCLUSIONS

The efficacy and safety of sevoflurane are well established. As the product is an inhalational gas, no bioequivalence study is required.

From a quality, non-clinical and clinical perspective, the overall assessment outcome of Sevoflurane 100% inhalational vapour liquid, is positive.

The SmPC is consistent with that of the reference product Sevorane 100%v/v Inhalation Gas marketed by AbbVie Limited in Ireland.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Sevoflurane 100% inhalational vapour liquid was the same as the reference product and therefore granted a marketing authorisation.

VI REVISION DATE

VII UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE