CBG MEB

Public Assessment Report

Scientific discussion

Sevofluraan Cadiasun 100%, inhalation vapour, liquid

(sevoflurane)

NL/H/2805/001/DC

Date: 18 November 2014

This module reflects the scientific discussion for the approval of Sevofluraan Cadiasun 100%, inhalation vapour, liquid. The procedure was finalised on 8 June 2014. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Sevofluraan Cadiasun 100%, inhalation vapour, liquid from Cadiasun Pharma GmbH.

The product is indicated for induction and maintenance of general anaesthesia in adult and paediatric patients of all ages, including full term neonates.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Sevorane, 100% inhalation vapour, liquid (NL License RVG 18395) which has been registered in the Netherlands by AbbVie B.V. since 1 September 1995.

The concerned member states (CMS) involved in this procedure were Germany and Spain.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Sevofluraan Cadiasun 100% is a clear, colourless, volatile liquid. The finished product is comprised only of the active ingredient.
The product is packed in type III, 250 ml amber coloured glass bottles with a yellow collar on the neck, sealed with a poly-seal black cap, and secured with PET film. The drug product needs to be vaporised in order to be administered; a vaporiser is not included.

II.2 Drug Substance

The active substance is sevoflurane, an established active substance described in European Pharmacopoeia. The active substance is a clear, colourless, volatile liquid, slightly soluble in water.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process consists of three steps: two synthetic steps and one purification step. No class 1 organic solvents and heavy metal catalysts are used. The proposed starting material and the specification thereof are acceptable and potential impurities have been adequately discussed.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. monograph, with no additional requirements. The specification is acceptable in view of the route of synthesis and the various European guidelines; all limits are adequately justified
Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale batches.

Stability of drug substance

Stability data on the active substance have been provided on three batches stored at 25°C/60% RH (34 months) and 40°C/75% RH (6 months). All parameters tested remain relatively stable at both storage conditions. Based on the stability data provided, the proposed re-test period of 24 months and the proposed storage conditions are considered acceptable.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described. The main development studies were manufacturing process development and the choice of the container closure system. No bioequivalence studies have been performed as the product is administered as gas and is identical to the innovator product. The compatibility of the drug product with vaporisers has been accurately discussed. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process consists of filling the active substance in the final package. The process has been adequately validated according to relevant European guidelines. The manufacturing process of the drug product is considered a non-sterile, standard process. Process validation data on the product has been presented for three pilot-scale batches. Process validation for full-scale batches will be performed post authorisation.

Quality control of drug product

The product specification includes tests for appearance, identification, acidity or alkalinity, refractive index, related substances, fluorides, non-volatile residue, water content and minimum fill. The release and shelf life limits are identical with the exception for identification which is not included in the shelf-life specification. The drug product specification is acceptable. The analytical methods been adequately described and validated.
Batch analytical data from the proposed production site have been provided on three pilot-scale batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided for three pilot-scale batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in amber glass bottles with poly-seal cap and PET film.
At accelerated conditions weight loss was observed, while at long term conditions no weight loss was observed. Furthermore an increase in non-volatile residue and water content was observed. The increase of water content was more pronounced at accelerated conditions. No differences were observed between upright and inverted position. All other parameters tested remained relatively stable throughout the test periods at both test conditions and within specification limits.
The proposed shelf life of 24 months without special storage conditions can be granted.

Based on the average duration of surgery, the complete bottle of 250 ml is not commonly used. Transfer of the complete contents of a bottle into the vaporiser is therefore not always the case in clinical practice. A single bottle may therefore be opened multiple times. In-use stability data has been provided demonstrating that the product remains stable for 5 days following first opening, when stored at 25ºC.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Sevofluraan Cadiasun 100%, inhalation vapour, liquid has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- The MAH committed to perform process validation studies on the first three commercial batches manufactured.
- The MAH committed to continue the on going long-term stability studies up to 36 months.

- The MAH committed to perform another in-use stability study on drug product which has been stored at the long-term storage conditions for at least 36 months if the stability data support the shelf life of 36 months.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Sevofluraan Cadiasun 100% is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Sevorane, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Sevoflurane is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

The product is administered via respiratory route (inhalation vapour, liquid), has no systemic activity and contains the same active substance as the innovator product. No bioequivalence studies have been submitted to support the application. Justification of biowaiver is provided based on the guideline (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/Corr **): If the product is a gas for inhalation, bioequivalence studies are not required.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Sevofluraan Cadiasun 100%, inhalation vapour, liquid.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Arrhythmia • Malignant hyperthermia • Seizures
Important potential risks	• QT prolongation • Post-operative hepatic dysfunction or hepatitis
Missing information	• Use in pregnancy • Use during lactation • Use in renal impairment

The member states agree that routine pharmacovigilance activities and routine risk minimisation activities are considered sufficient.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Sevorane. No new clinical studies were conducted, and risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The testing method included 24 participants and it was done in 3 stages: a pilot test with 4 participants, followed by two rounds with 10 participants each. The questionnaire contained 15 questions specific to Sevofluraan Cadiasun and 3 specific to the format of the package leaflet. The questions addressed all the key safety issues and concerns of Sevofluraan Cadiasun. There were no changes made to the PL based on any of the test rounds. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Sevofluraan Cadiasun 100%, inhalation vapour, liquid has a proven chemical-pharmaceutical quality and is a generic form of Sevorane 100%, inhalation vapour, liquid. Sevorane is a well-known medicinal product with an established favourable efficacy and safety profile

Since the product is administered via the respiratory route, has no systemic activity and contains the same amount of active substance as the innovator product, no bioequivalence study is deemed necessary.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Sevofluraan Cadiasun 100% inhalation vapour, liquid with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 8 June 2014.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached