CBG MEB

Public Assessment Report

Scientific discussion

Desfluraan Cadiasun 100% volatile liquid for administration by inhalation

(desflurane 100% v/v)

NL/H/3600/001/DC

Date: 25 October 2017

This module reflects the scientific discussion for the approval of Desfluraan Cadiasun 100%. The procedure was finalised on 8 March 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
USP	United States Pharmacopoeia

I. INTRODUCTION

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

The product is indicated for as an inhalation agent for maintenance of anesthesia for inpatient and outpatient surgery in intubated adults, infants and children.
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 Suprane 100% volatile liquid for administration by inhalation which has been registered in Germany by Baxter Deutschland GmbH since November 1994. The reference product in the Netherlands is Suprane (NL License RVG 17364) of Baxter B.V., registered since 26 April 1995.

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

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

II. QUALITY ASPECTS

II.1 Introduction

Desfluraan Cadiasun 100% is a clear, colourless, liquid.

The product is packed in 250-mL amber-coloured plastic coated glass bottles containing 240 mL of desflurane, sealed with a semi-transparent valve assembly and aluminum ferrule, and secured with PET sealing film.

The product does not contain excipients.

II.2 Drug Substance

The active substance is desflurane, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The drug substance is a clear, colourless, volatile liquid, which is practically insoluble 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 synthetic steps, and purification and filling steps No class 1 organic solvents are used. The proposed starting materials are acceptable. The drug substance manufacturing process, including quality control during manufacturing, is adequately described.

Quality control of drug substance
The drug substance specification of the MAH is in line with the ASMF-holder's specification - which is according to the Ph.Eur. monograph including tighter impurities limits, and with an additional requirement for microbial purity and assay. The specification is acceptable in view of the route of synthesis and the various European guidelines. All limits are adequately justified. The analytical methods in the drug substance specification of the MAH are generally according to those of the

ASMF-holder and the Ph. Eur. and the USP. USP methods have been cross-validated against the Ph. Eur. methods.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for three pilot scale batches.

Stability of drug substance
Stability data on the active substance have been provided three pilot scale batches stored at 30°C/60% RH (24 months) and 40°C/75% RH (6 months). All parameters tested remained stable at both storage conditions. Based on the stability data provided, the claimed re-test period of one year and “no special storage conditions” is justified.

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 the pure drug substance as a liquid which is administered after evaporation as a gas and is identical to the innovator product.
The compatibility of the drug product with vaporisers has been accurately discussed. Adequate results have been provided of a preservative efficacy test (Ph.Eur.) performed with the product. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of filling the drug substance in the final package. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three pilot scale batches. The product is manufactured using conventional manufacturing techniques. Process validation for full scaled batches will be performed post authorisation.

Quality control of drug product
The product specification includes tests for appearance, solubility, relative density, boiling point, identification, acidity or alkalinity, related substances, fluorides, non-volatile residue, water content, microbial purity, minimum fill/deliverable volume. The release and shelf life limits are identical. The drug product specification is acceptable. The analytical methods have 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 the proposed container closure system.
No significant changes were observed. All parameters tested remained relatively stable throughout the test periods at both test conditions and within specification limits.
The proposed shelf life of 24 months with as storage conditions no special storage conditions is justified.

Based on the average duration of surgery, the complete volume of the 250 ml bottle is not commonly used in clinical practice. A single bottle may therefore be opened multiple times. In-use stability data have been provided demonstrating that the product remains stable for 7 days following first opening, when stored at 25ºC.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Desfluraan Cadiasun has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.
No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Desfluraan Cadiasun 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 Suprane 100%, 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

Desflurane 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

Desfluraan Cadiasun is a volatile liquid for administration by inhalation, formulated to be identical to the originator product Suprane. The product contains the same concentration of desflurane as drug substance. In accordance with the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), no bioequivalence study has been conducted. This is acceptable for an inhalation gas.

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 Desfluraan Cadiasun.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Hepatic dysfunction • Malignant hyperthermia • Perioperative hyperkalemia • Cardiac arrhythmias • Myocardial ischemia in patients with history of coronary arty disease • Laryngospasm during maintenance of anesthesia in non-intubated children
Important potential risks	• Hypersensitivity reactions

	• Increased intracranial pressure in patients with space occupying lesions
Missing information	• Pregnant and lactating women and use during labor and vaginal delivery

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Suprane 100% volatile liquid for administration by inhalation. No new clinical studies were conducted. The indication initially applied for included induction of anaesthesia in adults, in line with the approved indication of the innovator product in Germany. However, this proposal was dropped as it is not an approved indication in the Netherlands.
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 questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
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

Desfluraan Cadiasun 100% volatile liquid for administration by inhalation has a proven chemical-pharmaceutical quality and is a generic form of Suprane 100%. Suprane 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 Desfluraan Cadiasun with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 8 March 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Procedure number	Scope	Product Information affected	Date of end of the procedure	Approval/ non approval	Summary/ Justification for refuse