Public Assessment Report

Scientific discussion

Sevofluran "Baxter" 100 % Inhalation vapour, liquid

Sevoflurane

DK/H/0784/001/E/001

This module reflects the scientific discussion for the approval of Sevofluran "Baxter". The procedure was finalised on 11 March 2010. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Sevofluran "Baxter" 100% inhalation vapour, liquid, from Baxter A/S, was first authorised in Denmark on 14 December 2004. Following national approval Denmark acted as reference member state in a mutual recognition procedure which was finalised on 1 August 2005. Following the first round MRP, the MAH sought recognition of the marketing authorisation by other Member States via a repeat use procedure. This report concerns the 2nd wave MRP.

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Sevofluran "Baxter" 100% inhalation vapour, liquid, from Baxter A/S. The product is indicated for induction and maintenance of general anaesthesia in adults and children.

Sevoflurane belongs to the halomethyl polyfluorisopropyl ether group of compounds and is structurally related to other inhaled volatile general anaesthetics, such as desflurane, enflurane and isoflurane. Sevoflurane is a very well established anaesthetic that was first developed in the 1960s and first approved in Japan in 1990. It is now marketed and has been used for several years as an anaesthetic in many countries worldwide including Japan, the European Economic Area (EEA), USA, Canada and Australia, for both day-care and inpatient paediatric and adult surgery.

This repeat use procedure concerns a generic application claiming essential similarity with the reference product Sevorane inhalation vapour, liquid, by Abbott Laboratories.

The marketing authorisation is granted based on article 10.1 of Directive 2001/83/EC.

Following finalisation of the first MRP the applicant has filed several variations. Also a renewal has been finalised.

The submitted dossier has been updated in accordance with the approvals.

II. QUALITY ASPECTS

II.1 Introduction

Sevofluran "Baxter" is a liquid inhalation vapour containing 100% sevoflurane.

The liquid is clear and colourless.

Sevofluran "Baxter" is packed in 250 ml aluminium bottles, lined with an internal epoxyphenolic resin protective lacquer, and plastic screw-on caps with a polytetraflurorethylene (PTFE) laminate inner liner. Pack sizes of 1 and 6 bottles have been approved. However, not all pack sizes may be marketed.

There are no excipients apart from the active substance.

Compliance with Good Manufacturing Practice

The RMS has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

II.2 Drug Substance

The product contains sevoflurane as active substance which is monographed in Ph.Eur. INN: Sevoflurane

Structural formula:

F₃C -OCH₂F F₂C

Sevoflurane is a clear, colourless, stable liquid containing no additives or chemical stabilizers. It is miscible with ethanol, ether, chloroform and petroleum benzene; and slightly soluble in water.

Two sources of sevoflurane are used. Information on the active substance is provided in full in the dossier and as a European Drug Master File in CTD format.

Details on the synthesis, starting materials, methods of analysis and their validations are all atisfactory. Impurities are adequately controlled. Specifications are satisfactory and test methods have been presented in adequate detail. Validation data are satisfactory. Based on the stability data, a suitable retest period has been set.

The applicant specification for sevoflurane is Ph.Eur. compliant and covers all potential impurities.

II.3 Medicinal Product

Product development *per* se is not actual as the product is exclusively active ingredient. Studies have been performed to investigate the suitability of the packaging materials. No incompatibilities have been observed. Sevoflurane is inherently antimicrobial.

Product manufacture consists of filling into primary containers. The process is suitably described, including relevant process parameters. There are no critical processes.

Validation data are not provided as the process is straightforward and the product is not required to be sterile.

The finished product specification is satisfactory.

Batch analysis data are provided for 3 pilot scale batches showing compliance with the release requirements and confirming consistency of product manufacture.

Stability data are provided for 4 batches of each strength stored in the proposed market packaging. A shelf-life of 2 years with no special storage precaution is approved.

III. NON-CLINICAL ASPECTS

Sevoflurane is a substance with well-known pharmacodynamic, pharmacokinetic and toxicological properties, which has been adequately summarised in the non-clinical overview. No new information is available which would from a toxicological point of view change the positive benefit/risk assessment of the substance. Specific studies have not been conducted in support of the application. This is considered acceptable as the present application is a generic application.

Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of sevoflurane released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

IV. CLINICAL ASPECTS

IV.1 Introduction

The proposed medicinal product is an inhalation vapour, liquid. The active ingredient (sevoflurane) is supplied as pure active ingredient. The submission of a bioequivalence study is not applicable according to chapter 5.1.7 of the "Note for guidance on the investigation of bioavailability and bioequivalence" (CPMP/EWP/QWP/1401/98).

IV.2 Risk management plan & Pharmacovigilance system

Sevoflurane was first approved in 1990, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of sevoflurane can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation.

The Pharmacovigilance system described fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the identification and notification of any a potential risks occurring either in the Community or in a third country.

V. PRODUCT INFORMATION

SmPC and Package leaflet

The content of the SmPC and package leaflet approved during the repeat use procedure is in accordance with that accepted during the renewal procedure.

Readability test

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 language used for the purpose of user testing the package leaflet was English. The test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. 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

Sevofluran "Baxter" 100% inhalation vapour, liquid, has a proven chemical-pharmaceutical quality and is a generic form of Sevorane inhalation vapour, liquid, by Abbott Laboratories. Sevorane is a well-known medicinal product with an established favourable efficacy and safety profile.

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

The SmPC, package leaflet and labelling are in the agreed templates and are in agreement with that accepted during the renewal procedure.

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The Concerned Member States, on the basis of the data submitted, considered that essential similarity has been demonstrated for Sevofluran "Baxter" with the reference product, and have therefore granted a marketing authorisation. The repeat use procedure was finalised on 11 March 2010.

A European harmonised birth date has been allocated (1990-01-23) and subsequently the first data lock point for sevoflurane is 2011-01. The next PSUR will cover the period from 1 January 2008 to 31 January 2011.

The common renewal date (CRD) is 21 October 2014. The marketing authorisation has previously been renewed according to the new legislation (Directive 2001/83/EC) for an unlimited period, however, in order to satisfy all member states, the applicant has accepted to submit another renewal application according to the CRD.

The following post-approval commitments have been made during the procedure:

A variation to change the SPC was submitted in line with the ongoing EU paediatric worksharing procedure for Suprane (desflurane) and has been withdrawn as the final report of this procedure has not been released by the rapporteur yet. The applicant has committed to apply for a new variation when the final report is released.

During the renewal procedure the applicant committed to update the SPC according to the SPC for sevoflurane when this is finalised.

Post-approval commitment as part of a variation to change the specification of an intermediate of the drug substance: provide batch data of 3 production batches of Sevofluran "Baxter", produced using the intermediate product with changed specification.