

**Rapporteur's
Public Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No1901/2006, as amended**

Sevoflurane

IE/W/002/pdWS/001

**Marketing Authorisation Holder:
ABBOTT**

Rapporteur:	Ireland
Start of the procedure (day 0):	01 September 2009
Date of this report:	05 November 2009
Deadline for Rapporteur's preliminary paediatric assessment report (PPdPAR) (day 70):	10 November 2009
Deadline for CMS's comments (day 85):	25 November 2009
Finalisation procedure (day 90):	30 November 2009

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section VII
INN (or common name) of the active substance(s):	Sevoflurane
MAH (s):	See section VII
Pharmaco-therapeutic group (ATC Code):	N01AB08
Pharmaceutical form(s) and strength(s):	Volatile liquid for inhalation
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I. EXECUTIVE SUMMARY

Sevoflurane is a clear, colourless, volatile liquid for inhalational anaesthesia, and is reported as being the most widely used volatile anaesthetic agent in the paediatric population. In accordance with Article 45 of the Paediatric Regulations 1901/2006, studies involving sevoflurane in the paediatric population have been submitted by the marketing authorisation holders. Analysis of these studies has not revealed any information which would change the current product information for sevoflurane. An assessment of the risk/benefit of sevoflurane remains positive.

No SPC changes are proposed.

II. RECOMMENDATION

As no significant additional information regarding the effects of sevoflurane in the paediatric population has been discovered as a result of this Article 45 procedure, no regulatory action is required. No changes to the Summary of Product characteristics or Package Leaflet are necessary.

III. INTRODUCTION

Several MAHs submitted 2 completed paediatric study(ies) for sevoflurane in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies) do not influence the benefit risk for sevoflurane and that there is no consequential regulatory action.

In addition, the following documentation has been included as per the procedural guidance:

- A line listing

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical study(ies)

Sevoflurane is a non-flammable volatile liquid for administration as an inhalational anaesthetic. There is no specific paediatric formulation, as different doses of the volatile liquid can be delivered by means of a specifically calibrated vaporiser.

IV.2 Non-clinical aspects

IV.2.1. Introduction

No non-clinical studies were submitted as part of this procedure.

IV.2.2. Non clinical study(ies)

N/A

IV.3 Clinical aspects

IV.3.1. Introduction

The MAH submitted 2 reports for:

- SEV-95-IT03 A prospective, randomised clinical comparison of sevoflurane and halothane in children;
- CHIN-05-001 An open-label, multi-center, phase IV study to evaluate the efficacy and safety profiles of sevoflurane in pediatric subjects of different ages undergoing inpatient surgery with general anesthesia.

IV.3.2. Clinical studies

SEV-95-IT03:

A prospective, randomised clinical comparison of sevoflurane and halothane in children;

➤ **Description**

A multicentre prospective randomised trial to compare the quality of induction, maintenance and recovery characteristics of halothane and sevoflurane when used in paediatric patients.

➤ **Methods**

- Objective(s)

To compare the quality of induction, maintenance and recovery characteristics of halothane and sevoflurane

- Study design

Multicentre prospective and randomised. Non-blinded.

- Study population /Sample size

Patients aged 3-12 years, ASA 1-2, elective surgery, 64 patients in total

- Treatments

All patients premedicated with flunitrazepam.

Induced with incremental increases in random volatile in N₂O/O₂.

- Outcomes/endpoints

Intubating conditions (3 point scale).

Use of Neuromuscular blockade to facilitate intubation.

Time points and intervals as follows:

- 1) From face mask application to loss of eyelash reflex (induction time)
- 2) From discontinuation of inhalational anaesthetic to extubation (extubation time)
- 3) Showing purposeful movement (response time)
- 4) Eye opening in response to non painful stimuli (emergence time)
- 5) Ready to be discharged from the recovery ward (discharging time)

- Statistical Methods

Study was powered to detect an 8 minute difference in emergence times between the two groups, accepting an error of 5% and an error of 20%.

Statistical analysis with SPSS 6.1.

Continuous variables: one-way analysis of variance (ANOVA), Student t or Mann Whitney U test.

Ordinal variables: contingency table analysis with χ^2 test.

P < 0.05 was considered significant.

➤ **Results**

- Recruitment/ Number analysed

64 patients enrolled; 32 per group. All were analysed.

No significant differences between the two groups.

- Baseline data

	Sevoflurane (n=32)	Halothane (n=32)
Age (years)	6.3 (3.6-12.3)	6.4 (3.1-11.0)
Weight (kg)	20 (14-60)	21 (14-47)
Height (cm)	117 (95-155)	116 (92-148)
Type of surgery (n.)		
— Urological	15	17
— Abdominal	14	8
— Orthopaedic	—	2
— Body surface	3	2
— ENT	—	3
Induction time (min)	2.0 (1-10)	3.0 (1-10)
Duration of anaesthesia (min)	31 (17-143)	39.5 (13-89)
Mean Integrated MAC (maintenance)	1.41 (1.09-2.27)	1.60 (0.77-2.00)
MAC hours	0.78 (0.28-3.63)	1.00 (0.43-1.63)

Results are expressed as median (range) or as number.

- Efficacy results

Non-significant difference in poor incubating conditions (sevoflurane = 1 Halothane = 3).

Significant reduction in emergence, response and discharge time with sevoflurane.

- Safety results

Significant reduction in heart rate during induction with halothane.

No other significant haemodynamic differences.

No differences in global adverse event rate, though significant increase in emergence agitation in sevoflurane group (3/32 vs/1/32, p < 0.05)

CHIN-05-001:

An open-label, multi-center, phase IV study to evaluate the efficacy and safety profiles of sevoflurane in paediatric subjects of different ages undergoing inpatient surgery with general anesthesia

➤ **Description**

This was a single agent, open label multicentre trial to assess the efficacy and safety profile of sevoflurane in patients of differing ages undergoing elective surgery lasting from 1 to 3 hours. All patients were between 3 and 10 years of age, and were all healthy (ASA status 1 and 2).

➤ **Methods**

- Objective(s)

- 1) To evaluate the induction and emergence characteristics of sevoflurane in paediatric subjects.
- 2) To determine if differences exist in induction and emergence characteristics for different age groups of paediatric subjects.
- 3) To evaluate the safety of sevoflurane in paediatric subjects.

- Study design

Open-label, single arm multi-centre phase IV trial.

- Study population /Sample size

285 ASA 1 and 2 paediatric subjects between 3 and 10 years undergoing in-patient elective surgery expected to last 1 – 3 hours.

- Treatments

Inhalational anaesthesia with sevoflurane, increased in an incremental manner.

- Outcomes/endpoints

Efficacy Primary:

Emergence time (time from cessation of sevoflurane to eye opening).

Efficacy Secondary:

- 1) Induction time (from beginning of sevoflurane administration to loss of eyelash reflex).
- 2) Relationship between time to eye opening and MAC-hours of anaesthetic agent.
- 3) Time from cessation of agent to achievement of a modified Aldrete score of 9 in the PACU.
- 4) Time from cessation of sevoflurane to tracheal administration.

Safety:

- 1) Vital signs (temperature heart rate respiratory rate blood pressure).
- 2) Complications during induction (coughing, breath holding excitement, secretions).
- 3) Postoperative nausea and vomiting in the PACU.
- 4) Adverse event collection.

- Statistical Methods

Efficacy/Safety:

All efficacy and safety analyses were performed on Intent-to-Treat (ITT) population. The ITT population included all enrolled subjects who consumed any of the study drug.

Demographics and baseline characteristics were tabulated.

Times to induction, eye opening, tracheal extubation and achievement of Aldrate score of 9 were summarized by mean, standard deviation, 25% quantiles (Q1), median, 75% quantiles (Q3) and range.

The correlations between age and times to induction, eye opening, tracheal extubation and achievement of Aldrate score of 9 were investigated by plotting, and by regression analysis, Pearson Correlation Coefficients and P-values were calculated. Sub-group analyses were performed by dividing subjects into the age 3-6 years group and the age 7-10 years group, comparison of the primary and secondary efficacy variables between the groups was performed using analysis of variance (ANOVA) with age group and centre as factors.

Regression analyses were also used to evaluate the correlation between the amount of anaesthetic agent administered as measured by MAC-hours and the time to eye opening.

Incidences of treatment-emergent adverse events were summarized by MedDRA preferred term, relationship to study agent, and intensity. Complications during the induction and post-anaesthetic nausea and vomiting in the PACU were summarized.

➤ **Results**

- Recruitment/ Number analysed

285 subjects recruited; 284 completed the study (withdrawal due to changes surgical procedure)

- Baseline data

Characteristics	SEVOFLURANE (N=285)
Gender, n (%)	
Male	196 (68.8)
Female	89 (31.2)
Age, (yrs)	
N	285
Mean	5.3
SD	2.1
Median	5.0
Range (Min,Max)	(3,10)
Age Class, n (%)	
3-6 yrs	203 (71.2)
7-10 yrs	82 (28.8)
Height, (cm)	
N	285
Mean	108.8
SD	17.7
Median	108.0
Range (Min,Max)	(70,152)

- Efficacy results

The study showed a significantly shorter time to eye-opening in the 3-6 group than the 7-10 group (p=0.041), and this result was confirmed by regression analysis.

There were no statistical differences between the two groups in relation to the secondary endpoints of induction time, time to modified Aldrete score of 9, and time to tracheal extubation. There was a significant correlation between time to eye-opening, and amount of anaesthetic agent consumed.

- Safety results

Of 285 dosed patients, 47 (16.5%) experienced at least one adverse event. 44 of which were determined to be at least possibly related to the agent. The majority of events were classified as either mild or moderate, with one severe adverse event (agitation) reported. The majority (34/47) of adverse events related to restlessness, and the majority (34/47) of events occurred during induction. No subject was discontinued from the study medication due to adverse events, and there were no serious adverse events.

Discussion on clinical aspects:

The results of this study are consistent with previous experience of sevoflurane in this age group. No new safety information was discovered by this study.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

➤ **Overall conclusion**

The information gained from the clinical trials submitted as part of this Article 45 application is consistent with that currently known about the medicinal product. The risk/benefit of this product remains positive, and no changes to the product information are required.

➤ **Recommendation**

No further action required.

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

Not applicable.