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

Isoflurane

UK/W/072/pdWS/001

Rapporteur:	UK
Finalisation procedure (day 120):	24th April 2015

TABLE OF CONTENTS

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section X
INN (or common name) of the active substance(s):	Isoflurane
MAH (s):	See section X
Pharmaco-therapeutic group (ATC Code):	N01AB06
Pharmaceutical form(s) and strength(s):	Inhalational anaesthetic Isoflurane 99.9% w/w

I. EXECUTIVE SUMMARY

This is a data submission for isoflurane in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use. The UK is the rapporteur for this procedure.
One MAH has submitted data that include published articles regarding the use of isoflurane in paediatric clinical studies.
Isoflurane is a difluoromethyl ether inhalation anaesthetic which may be used for the induction and maintenance of general anaesthesia in adult and paediatric patients.

The MAH has highlighted paediatric data present in the currently approved UK Summary of Product Characteristics (SmPC) and Package Information Leaflet (PIL), and the MAH has proposed to include this information in all the EU labels.

Additionally, during this work-sharing procedure, one member state sent comments questioning the use of isoflurane for induction of anaesthesia in children. Advice from the European Society for Paediatric Anaesthesiology and Association of Anaesthetists of Great Britain and Ireland was sought in order to clarify the clinical use of isoflurane for induction of anaesthesia in children.

Taking into account the submitted data package, comments received from member states and the advice received from the anaesthetic expert groups, the rapporteur concludes that important paediatric information should be added to the product information of all isoflurane containing products. This will include the addition of paediatric safety information, supported by submitted data, in sections 4.4 and 4.8. Additionally, in line with available literature, current clinical practice and expert advice, the rapporteur proposes to include wording in section 4.2 to indicate that the use of isoflurane is not recommended for induction of anaesthesia in children.

II. RECOMMENDATION

SmPC changes are proposed in sections 4.2, 4.4, 4.8 and PIL changes are proposed in sections 3 and 4.

Summary of outcome

- ☐ No change
- ☒ Change
  - ☐ New study data
  - ☐ New safety information
  - ☒ Paediatric information clarified <section 4.2>
  - ☐ New indication

The final SmPC and PIL recommendations are presented below:

SUMMARY OF PRODUCT CHARACTERISTICS

Section 4.2 Posology and method of administration

[This section should be amended to include the below wording]

[…]

ADULTS*		
Age	**Average MAC Value In 100% Oxygen**	**70% N_2O**
26 ± 4 years	1.28%	0.56%
44 ± 7 years	1.15%	0.50%
64 ± 5 years	1.05%	0.37%

PAEDIATRIC POPULATION	
Age	**Average MAC Value In 100% Oxygen**
Preterm neonates < 32 weeks gestational age	1.28%
Preterm neonates 32-37 weeks gestational age	1.41%
0-1 month	1.60%
1-6 months	1.87%
6-12 months	1.80%
1-5 years	1.60%

Premedication: Drugs used for premedication should be selected for the individual patient bearing in mind the respiratory depressant effect of isoflurane. The use of anticholinergic drugs is a matter of choice, but may be advisable for inhalation induction in paediatrics.

Induction of anaesthesia in children:
Isoflurane is not recommended for use as an inhalation induction agent in infants and children because of the occurrence of cough, breath-holding, desaturation, increased secretions and laryngospasm (see section 4.4).

*[*Rapporteur's comment: The information in the table corresponding to adult use should remain unchanged as currently approved in SmPCs as it is outside the remit of this European Paediatric work-sharing procedure under Article 45. Additionally, according to the European Commission A guideline on SmPC (September 2009), "each section of the SmPC should first deal with those issues that apply to the core population for whom the medicine is indicated followed - when necessary – by specific information for any relevant special population (e.g. children)." Therefore, the MAC values for adults appear at the top of the table, followed by the MAC values for children under the sub-heading 'PAEDIATRIC POPULATION'.]*

Section 4.4 Special warnings and precautions for use

[This section should be amended to include the below wording]

During the induction of anaesthesia, saliva flow and tracheobronchial secretion can increase and can be the cause of laryngospasm, particularly in children.

Perioperative Hyperkalaemia
Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period. Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable. Concomitant use of succinylcholine has been associated with most, but not all, of these cases. These patients also experienced significant elevations in serum creatine kinase levels and, in some cases, changes in urine consistent with myoglobinuria. Despite the similarity in presentation to malignant hyperthermia, none of these patients exhibited signs or symptoms of muscle rigidity or hypermetabolic state. Early and aggressive intervention to treat the hyperkalaemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease.

Section 4.8 Undesirable effects

[This section should be amended to include the below wording]

Paediatric population
Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period (see section 4.4).

Other special populations
Neuromuscular disease:
Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period. Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable. Early and aggressive intervention to treat the hyperkalaemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease (see section 4.4).

PACKAGE INFORMATION LEAFLET

Section 3 - How will you receive Isoflurane?

[This section should be amended to include the below wording]

Isoflurane will ALWAYS be administered to you by an anaesthetist. They will decide on the dose you will receive, depending on your age, weight and the type of operation you are having.

Your child should be monitored closely during the administration of Isoflurane *[Rapporteur's comment: This statement may be added if the corresponding paediatric statement is already included in the SmPC]*

Inducing sleep at the start of anaesthesia
Isoflurane is not recommended in infants and children for inducing sleep at the start of anaesthesia.

Medication before anaesthesia
Anaesthetist may decide to give your child medication to counter act the possible reduction in breathing and heart rate effects which may occur with the use of Isoflurane.

Section 4 - What will happen after receiving Isoflurane?

[This section should be amended to include the below wording]

If you or your child suffer from any unusual or unexpected symptoms after an operation tell your doctor or anaesthetist IMMEDIATELY.

The most commonly reported side effects are:

- A tightening of your lungs and airways causing a difficulty in breathing
- Increases in blood sugar levels or potassium levels. There have been rare reports of abnormal heartbeat (arrhythmias) and death associated with the use of inhaled anaesthetics in children shortly after surgery

---

The applicant is therefore requested to submit a Type IB variation to update the SmPCs and PILs of isoflurane containing products in line with the above work-sharing recommendations within 60 days of this report.

III. INTRODUCTION

On 17.04.2014, one MAH submitted paediatric data regarding isoflurane, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

The following documentation has been included as per the procedural guidance:

- Published articles regarding the use of isoflurane in paediatric clinical studies.

- A critical expert overview of the paediatric data.

- Currently approved UK SmPC and PIL
  - With the approved paediatric data highlighted which the MAH propose to include in all the EU labels.

- Relevant PSUR data.

- Currently approved Company Core Data Sheet (As supportive documentation).

Overview of currently approved UK SmPC and PIL

The currently approved UK SmPC includes paediatric data which the MAH proposes to add to all the EU SmPCs. Sections of the currently approved UK SmPC of isoflurane are presented below:

Section 4.2 Posology and method of administration

Vaporisers specially calibrated for isoflurane should be used so that the concentration of anaesthetic delivered can be accurately controlled.
MAC values for isoflurane vary with age. The table below indicates average MAC values for different age groups.

Age	Average MAC Value In 100% Oxygen	70% N_2O
0-1 month	1.60%	
1-6 months	1.87%	
6-12 months	1.80%	
1-5 years	1.60%	
26 ± 4 years	1.28%	0.56%
44 ± 7 years	1.15%	0.50%
64 ± 5 years	1.05%	0.37%

Premedication: Drugs used for premedication should be selected for the individual patient bearing in mind the respiratory depressant effect of isoflurane. The use of anticholinergic drugs is a matter of choice, but may be advisable for inhalation induction in paediatrics.

Section 4.4 Special warnings and precautions for use

During the induction of anaesthesia, saliva flow and tracheobronchial secretion can increase and can be the cause of laryngospasm, particularly in children.

Children Under Two Years of Age
Caution should be exercised when isoflurane is used in small children due to limited experience with this patient-group.

Perioperative hyperkalaemia
Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period. Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable. Concomitant use of succinylcholine has been associated with most, but not all, of these cases. These patients also experienced significant elevations in serum creatine kinase levels and, in some cases, changes in urine consistent with myoglobinuria. Despite the similarity in presentation to malignant hyperthermia, none of these patients exhibited signs or symptoms of muscle rigidity or hypermetabolic state. Early and aggressive intervention to treat the hyperkalaemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease.

Section 4.8 Undesirable effects
d. Paediatric population
Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period. (See 4.4.)

e. Other special populations
Neuromuscular disease:
Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period. Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable. (See 4.4.)

Patient Information Leaflet (PIL)
The paediatric information that is currently in the approved UK PIL, which the MAH proposes to include in all the EU PILs is displayed below (paediatric data in ***bold italics***).

1. What is isoflurane and what does it do?
   - Once breathed in (inhaled), Isoflurane will induce and maintain a deep, pain-free sleep (general anaesthesia) in adults ***and children.***

Rapporteur's comments:
The MAH did not discuss the regulatory status of isoflurane in other EU countries and did not provide other country-specific SmPCs/PILs of isoflurane.
The MAH proposes to add paediatric data currently present in the UK SmPC to all EU SmPCs. The Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) has published 'Recommendations on submission & assessment in paediatric worksharing' (*CMDh/141/2009/Rev2 – March 2013)* which state that *"Where there are differences in the product information registered in different MS, it is the responsibility of the MAH to consider how to address this situation, taking into account that it is an objective of the Paediatric Regulation to give children the same access to authorised medicinal products suitable for their use across the European Community. The MAH may consider a range of regulatory options including submission of a series of variations or initiation of a referral procedure in order*

to achieve a harmonised position. The MAH should note that the paediatric work-sharing procedure is not a basic harmonisation process."

The rapporteur has reviewed the data submitted by the MAH as part of this work-sharing procedure. It has been noted that the currently approved UK SmPC already contains significantly detailed paediatric information. Most of the MAH's SmPC recommendations are supported by the data submitted as part of this European paediatric work-sharing procedure under Article 45 of the Paediatric Regulation. Therefore, the rapporteur is making recommendations for important paediatric information, supported by the submitted data, to be added (if not already included) in corresponding sections of the SmPC for all isoflurane products.
The submitted data are further discussed in section IV.3 Clinical aspects, and the recommendations are listed in section X Rapporteur's final conclusion and recommendation.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical studies

Isoflurane, a non-flammable liquid administered by vaporization, is a general inhalation anaesthetic drug with a mildly pungent ethereal odour. No additive or stabilizer is present.
It is identified chemically as 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether and its molecular weight is 184.5. Isoflurane has been reported to have favourable properties of fast uptake and elimination coupled with minimal biotransformation.

Isoflurane is indicated for induction and maintenance of general anaesthesia.
Vaporizers specially calibrated for isoflurane should be used so that the concentration of anaesthetic delivered can be accurately controlled.

Rapporteur's comments:
The MAH has not provided any information on the pharmaceutical formulation used in the submitted paediatric clinical studies.

IV.2 Non-clinical aspects

The MAH stated that it does not hold any data on quality and non-clinical paediatric studies.

Rapporteur's comments:
No preclinical information relevant to the paediatric population is available in the currently approved UK SmPC of isoflurane.

The United States Package Insert (USP) of isoflurane has the following non-clinical information:
"Carcinogenesis, Mutagenesis, Impairment of Fertility
Swiss ICR mice were given isoflurane to determine whether such exposure might induce neoplasia. Isoflurane was given at ½, ⅛ and 1/32 MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice, which were given the same background gases, but not the anesthetic.

Pregnancy
Pregnancy Category C

Isoflurane has been shown to have a possible anesthetic-related fetotoxic effect in mice when given in doses 6 times the human dose. There are no adequate and well-controlled studies in pregnant women. Isoflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."

IV.3 Clinical aspects

1. Clinical overview

Minimum Alveolar Concentration (MAC) Values in Paediatric Patients

Anaesthetic potency for volatile anaesthetics is measured in minimum alveolar concentration (MAC) units, with 1 MAC defined as the minimum alveolar concentration that prevents movement in response to surgical stimulation in 50% of subjects. The MAC potency is dependent on age, with younger patients generally requiring higher MAC values and older patients requiring lower MAC values for a given depth of anaesthesia.

The MAH reported that the anaesthetic potency of isoflurane is intermediate between halothane and enflurane or sevoflurane. It has a MAC value of 1.15% in middle-aged adults. MAC of isoflurane is higher in children than in adults and decreases with age.

Section 5.2 'Pharmacokinetic properties' of the UK SmPC of isoflurane provides the following information:

MAC (Minimum Alveolar Concentration in man):

Age	100% Oxygen	70% N_2O
26 ± 4	1.28	0.56
44 ± 7	1.15	0.50
64 ± 5	1.05	0.37

Indications and dose

The UK SmPC of isoflurane has the following information on indications and dose:

Induction: A short-acting barbiturate or other intravenous induction agent is usually administered followed by inhalation of the isoflurane mixture. Alternatively, isoflurane with oxygen or with an oxygen/nitrous oxide mixture may be used.
It is recommended that induction with isoflurane be initiated at a concentration of 0.5%.
Concentrations of 1.5 to 3.0% usually produce surgical anaesthesia in 7 to 10 minutes.

Maintenance: Surgical levels of anaesthesia may be maintained with 1.0-2.5% isoflurane in oxygen/nitrous oxide mixtures. An additional 0.5-1.0% isoflurane may be required when given with oxygen alone.
For caesarean section, 0.5-0.75% isoflurane in a mixture of oxygen/nitrous oxide is suitable to maintain anaesthesia for this procedure.

Rapporteur's comments:
The British National Formulary for children (BNF-c) 2014-2015 lists the indications and dose of isoflurane as follows:

Induction of anaesthesia
•By inhalation through specifically calibrated vaporiser

Neonate increased gradually according to response from 0.5–3% in oxygen or nitrous oxide-oxygen
Child 1 month–18 years increased gradually according to response from 0.5–3% in oxygen or nitrous oxide-oxygen

Maintenance of anaesthesia
•By inhalation through specifically calibrated vaporiser
Neonate 1–2.5% in nitrous oxide-oxygen; additional 0.5–1% may be required if given with oxygen alone
Child 1 month–18 years 1–2.5% in nitrous oxide-oxygen; additional 0.5–1% may be required if given with oxygen alone; caesarean section, 0.5–0.75% in nitrous oxide-oxygen

The rapporteur notes that the indications and dose in BNF-c are in line with the UK SmPC information.

2. Clinical studies

MAC of isoflurane for paediatric age groups

The MAH described three clinical studies that investigated the MAC of isoflurane in several paediatric age groups. These clinical studies that are available from published literature are summarised in Table 1 below:

Table 1. MAC of isoflurane for several paediatric age groups

Study Number/Lead Author/Title	Study Design/Method	N	Baseline Characteristics	Results/Conclusions
Cameron CB, Robinson S, Gregory GA. The minimum anesthetic concentration of isoflurane in children. Anesth Analg. 1984;63:418-20.	Open-label, dose-finding: first patient in each of five groups was given an isoflurane concentration of 1.3% after induction. Upon surgical incision, if patient movement was detected then subsequent patient given next highest value (increase 0.2%), or if no movement then subsequent patient given next lowest value (decrease 0.2%).	60	Five groups (12 per group): 0 – 1 month (neonates) 1 – 6 months 6 – 12 months 1 – 3 years 3 – 6 years	MAC values for patients studied were determined to be: 0 – 1 month (neonates): 1.60% ± 0.01 1 – 6 months: 1.87% ± 0.12 6 – 12 months: 1.80% ± 0.01 1 – 3 years: 1.60% ± 0.16 3 – 5 years: 1.60% ± 0.06 (*P* < 0.001).
LeDez, KM, Lerman J. The minimum alveolar concentration (MAC) of isoflurane in preterm neonates.	Open label, dose finding. Following tracheal intubation and anesthetization, the move-no move responses to skin incision were recorded, and MAC	36	Two groups: Group 1 (20): preterm < 32 weeks gestation Group 2 (16): 32 – 37 weeks gestation All patients were < 1 month old.	The MAC (± SD) of isoflurane was significantly less in neonates < 32 weeks gestation, 1.28 ± 0.17% than in neonates 32 – 37 weeks gestation, 1.41 ± 0.18% (*P* < 0.05). Conclusion: Isoflurane is a

<table>
<tr><td>Anesthesiology. 1987;67:301-7.</td><td>was determined using the "up-and-down" technique of increasing or decreasing dosing, as indicated in the above publication.</td><td></td><td></td><td>safe and reliable anesthetic which maintains systolic arterial pressure within the normal range in preterm neonates.</td></tr>
<tr><td>Murray DJ, Mehta MP, Forbes RB. The additive contribution of nitrous oxide to isoflurane MAC in infants and children Anesthesiology. 1991;75:186-90.</td><td>Open-label dose finding.
Each patient was observed for purposeful movement, i.e., movement of the head or upper or lower extremities in the 30-s period after skin incision. If movement detected, subsequent patient isoflurane concentration increased by 0.2%, if movement not detected subsequent patient isoflurane concentration decreased by 0.2%.</td><td>47</td><td>Four groups:
100% O2 n = 11
75% O2/25% N_2O n = 12
50% O2/50% N_2O n = 12
25% O2/75% N_2O n = 12</td><td>MAC values of isoflurane for patients receiving various concentrations of N_2O were determined to be:
<table><tr><th>N_2O %</th><th>MAC</th></tr><tr><td>0</td><td>1.69 ± 0.13</td></tr><tr><td>25</td><td>1.26 ± 0.10</td></tr><tr><td>50</td><td>0.97 ± 0.10</td></tr><tr><td>75</td><td>0.58 ± 0.09</td></tr></table></td></tr>
</table>

Rapporteur's comments:

The MAH considered the Cameron et al study (1984) to be the key study that determined the MAC values for different paediatric subgroups. The data form the background evidence of MAC values currently listed in the UK SmPC of isoflurane for children between the ages of 0 months to 5 years.

This study was an open-label, dose finding study that investigated the MAC of isoflurane in five age groups. There were 12 patients in each group. The results showed that the MAC was 1.60% ± 0.01 for patients who were 0-1 month of age (neonates); 1.87% ± 0.12 for those 1-6 months of age, 1.80% ± 0.01 for those 6-12 months of age, 1.6% ± 0.16 for those 1-3 year of age, and 1.60% ± 0.06 for children 3-5 years of age ($p < 0.001$).

The rapporteur considers that this study provides supporting data for MAC values of isoflurane in children 0 months and 5 years and recommends that the MAC values be added to section 4.2 Posology and method of administration of SmPCs (if not currently included).

LeDez KM and Lerman J (1987) determined the MAC of isoflurane in two groups of preterm neonates less than 1 month post-natal age who were either <32 weeks or 32-37 weeks gestational age. The MAC (± SD) of isoflurane was significantly less in neonates < 32 weeks gestation, 1.28 ± 0.17% than in neonates 32 – 37 weeks gestation, 1.41 ± 0.18% ($P < 0.05$). From the literature article, the rapporteur also notes that the heart rate of the neonates did not decrease significantly in either group during the study. Systolic arterial pressure decreased between 20 and 30% below awake values both before and after skin incision in both age groups (*P<0.01*). Intravenous administration of balanced salt solution or plasma restored the systolic arterial pressure to acceptable values (i.e., ≥40 mmHg).

From the UK SmPC of isoflurane and the Cameron et al study (1984), the rapporteur notes that the MAC value of isoflurane in children aged 0 – 1 month (neonates) is: 1.60% ± 0.01. In

comparison, LeDez KM and Lerman J (1987) demonstrated that the MAC (± SD) of isoflurane in neonates < 32 weeks gestation was 1.28 ± 0.17% and the MAC (± SD) of isoflurane in neonates 32-37 weeks gestation was 1.41 ± 0.18% ($P < 0.05$).
The rapporteur notes that preterm neonates in the gestational age groups <32 weeks gestation and 32-37 weeks gestation appear to have lower MAC values compared to the MAC value of neonates quoted in the Cameron et al study (1984) and UK SmPC.
The MAH is requested to provide an overview of all available data evaluating the MAC values of isoflurane in preterm neonates and to consider if the data can support inclusion of MAC values of preterm neonates in the SmPC.

Murray et al (1991) determined the contribution of nitrous oxide to isoflurane MAC in a study of 47 paediatric patients with mean ages 16.6 ± 6.7 months. The authors reported that the MAC value for isoflurane in oxygen in this study (1.69 ± 0.13%) was similar to the MAC reported by Cameron et al (1984) in infants (6-12 months old) and children (1-3 years old), for whom MAC was 1.8 and 1.6% respectively. The authors also reported that as the concentration of nitrous oxide increased, the MAC of isoflurane decreased linearly.
The rapporteur notes that for adults, the MAC values of isoflurane with concomitant 70% concentration of nitrous oxide are reported in the UK SmPC of isoflurane. However, the MAC values of isoflurane in the presence of nitrous oxide are not specified for paediatric age groups.

Table of MAC values from UK SmPC of isoflurane:

Age	Average MAC Value In 100% Oxygen	70% N_2O
0-1 month	1.60%	
1-6 months	1.87%	
6-12 months	1.80%	
1-5 years	1.60%	
26 ± 4 years	1.28%	0.56%
44 ± 7 years	1.15%	0.50%
64 ± 5 years	1.05%	0.37%

The MAH is requested to provide an overview of data evaluating MAC values of isoflurane with concomitant concentration of nitrous oxide for different paediatric age groups and to consider whether the data are robust enough to add the MAC values of isoflurane in the presence of nitrous oxide to the SmPC.

Based on the three clinical studies submitted, the rapporteur concludes that although the data support the currently approved indications, the data do not demonstrate new evidence on the efficacy of isoflurane in the paediatric population.

Cardiovascular effects of isoflurane

Additionally, the MAH presented three clinical studies that describe the cardiovascular effects of isoflurane on infants and children.

Table 2. Cardiovascular effects of isoflurane on infants and children.

Study Number/Lead Author/Title	Study Design/Method	N	Baseline Characteristics	Results/Conclusions
Friesen RH, Lichtor JL. Cardiovascular effects of	Open-label, randomized. Patients were randomly assigned	60	Two groups of 30 infants aged 5 – 26 weeks scheduled for elective surgical procedures were	Patients in Group 1 had a 32% decrease in HR. This decrease was significantly ($P < 0.01$) reduced to

inhalation induction with isoflurane in infants. Anesth Analg. 1983;62(4):411-4.	into one of two groups: Group 1: non-premedicated Group 2: premedicated with 0.02 mg/kg of atropine given intramuscularly 25 – 60 minutes before induction of anesthesia Anesthesia induction performed with isoflurane in both groups. Blood pressure (BP), heart rate (HR), and mean arterial pressure (MAP) recorded at 1-minute intervals for 20 minutes.		studied. All were ASA status I or II without known cardiac or pulmonary disease. There were no significant differences between the two groups of infants with respect to age, weight, haematocrit, fasting time, and physical status	20% by premedication with atropine in Group 2. Decreases in MAP and BP values were not significantly different between the groups. Conclusion: During isoflurane induction in infants, both HR and BP are depressed. Premedication with atropine minimizes the depression of HR, but does not affect the change in BP.
Lopez-Gil M, Brimacombe J, Alvarez M. Maranon University Hospital, Madrid, Spain. Safety and efficacy of the laryngeal mask airway. A prospective survey of 1400 children. Anaesthesia. 1996;51(10):969-72.	A survey of laryngeal mask airway usage in 1400 infants and children by 10 trainee anaesthetists to provide information about insertion and complication rates using the standard insertion technique and a limited range of standardized anesthetic techniques, using isoflurane or total intravenous anesthesia.	1400	All patients were ASA grade 1~3 and the male to female ratio was 1.9:l. The mean (range) for age and weight was 6.25 (0 – 18) years and 28.9 (2 – 70) kg, respectively. The mean (range) duration of procedures was 40 (5 – 260) minutes.	Placement was successful in 90% (1258/1400) at the first attempt, 8% (112/1400) at the second attempt and 2% (29/1400) required an alternative technique of insertion. Conclusion: The laryngeal mask provides a safe and effective form of airway management for infants and children in the hands of supervised anaesthesia trainees both for spontaneous and controlled ventilation using either isoflurane or total intravenous anaesthesia.
Shaw CA, Kelleher AA, Gill CP, Murdoch LJ, Stables RH, Black AE. Comparison of the incidence of complications at induction and emergence in infants receiving oral atropine vs no premedication. Br J Anesth.	Open-label, randomized. Patients were randomised to receive oral atropine (Group A) or no premedication (Group B) 1 hour prior to operation.	120	Patients less than 1 year of age, ASA I or II undergoing elective surgery which required tracheal intubation as part of anesthetic technique. All patients underwent a standardized anaesthetic, including inhalation induction. Patients with a history of airway problems were excluded.	There were significantly more airway complications in Group B (no premedication) both at induction and emergence (25% and 49% respectively, compared with 9% and 25% in Group A; $p < 0.015$). Conclusion: The incidence of airway complications at induction and emergence was reduced by orally administered atropine premedication.

2000;84(2):174-8				

Rapporteur's comments:
Friesen RH and Lichtor JL (1983) showed that induction of isoflurane anaesthesia in infants 5-26 weeks of age was associated with significant decreases in HR, BP, and MAP. Premedication with atropine minimized the depression of HR, but did not affect the change in BP.
From the literature article, the rapporteur notes that moderate to severe laryngospasm occurred during induction in 12 infants in group 1 and 7 infants in group 2. The authors reported that laryngospasm was associated with copious pharyngeal secretions and generally occurred before laryngoscopy. Positive airway pressure was the method of management used with success in all cases of laryngospasm.
This study provides evidence that during the induction of anaesthesia with isoflurane, laryngospasm associated with copious pharyngeal secretions may occur in children. Based on this submitted study, the rapporteur recommends that the paediatric information on laryngospasm should be added to section 4.4 Special warnings and precautions for use of SmPCs (if not currently included).

Proposed SmPC wording (as currently in section 4.4 of the UK SmPC):
During the induction of anaesthesia, saliva flow and tracheobronchial secretion can increase and can be the cause of laryngospasm, particularly in children

Friesen RH and Lichtor JL (1983) also reported that there were significantly more airway complications in patients who did not receive premedication with atropine at both induction and emergence. The authors concluded that the incidence of airway complications at induction and emergence was reduced by orally administered atropine premedication.
This study supports the need for appropriate wording on 'Premedication' in section 4.2 of the SmPC and the rapporteur recommends that this statement be added to SmPCs (if not currently included):

Proposed SmPC wording (as currently in section 4.2 of the UK SmPC):
Premedication: Drugs used for premedication should be selected for the individual patient bearing in mind the respiratory depressant effect of isoflurane. The use of anticholinergic drugs is a matter of choice, but may be advisable for inhalation induction in paediatrics.

Lopez-Gil et al (1996) described a survey of laryngeal mask airway usage in 1400 infants and children to provide information about insertion and complication rates using the standard insertion technique for laryngeal mask airway. In this survey, anaesthesia was maintained with either isoflurane or intravenous propofol. The authors concluded that the laryngeal mask provided a safe and effective form of airway management for infants and children in the hands of supervised anaesthesia trainees using either isoflurane or total intravenous anaesthesia. The safety and efficacy of isoflurane was not further discussed.

In the study by Shaw et al (2000), inhalational induction was done with halothane. The incidence of airway complications at induction and emergence was reduced by orally administered atropine premedication. As isoflurane was not used in this clinical trial, this study will not be discussed further.

The rapporteur concludes that the above studies provide important safety information in the paediatric population that need to be reflected in all SmPCs of isoflurane containing products across the EU (if not already included).

3. Clinical safety

The MAH completed an aggregate review of the Periodic Safety Update Reports (PSURs) for the period of 01 January 1993 through 06 October 2011. A total of 112 paediatric (<18 years of age) case reports were identified. The most frequently identified adverse events throughout the series were malignant hyperthermia, bronchospasm, and cardiac arrest.
The MAH concluded that overall, the adverse events reported from the paediatric population were consistent with the current Company Core Data Sheet (CCDS) for isoflurane.

Rapporteur's comments:
The rapporteur identified the fatal cases from the aggregate review of the PSURs and these are further presented in Table 3 below:

Table 3. Fatal cases from cumulative isoflurane PSURs: 01 Jan 1993 – 06 Oct 2011

PSUR	Fatal cases	MAH comments
PSUR 1 (01 Jan 1993 – 31 Dec 1997)	There was 1 fatal report of a 17-year-old male subject resulting from a pulmonary embolus.	No new safety issues have arisen concerning special patient groups.
PSUR 2 (01 Dec 1996 – 10 Sep 2001)	There were two fatal case reports involving a 13-year-old male with an arrhythmia/cardiac arrest and a 16-year-old male with an event of malignant hyperthermia.	No new safety issues have arisen concerning special patient groups. Overall, the adverse reactions reported from this patient population were consistent with the current CCDS.
PSUR 3 (11 Sep 2001 – 11 Aug 2006)	There were two fatal case reports received, both involved 5-year-old male subjects for the events of malignant hyperthermia and cardiac arrest secondary to rhabdomyolysis respectively.	Overall, the adverse reactions reported from this patient population were consistent with the current CCDS.
PSUR 4 (12 Aug 2006 – 06 Oct 2008)	There were no reports with a fatal outcome.	Based on the analysis of reports of patients ≤18 years of age, no new safety signal was identified and no changes to the current CCDS were recommended.
PSUR 5 (07 Oct 2008 – 06 Oct 2011)	There were four reports with a fatal outcome. The first report involved a 3-year-old male having a shunt revision resulting in an increased intracranial pressure necessitating emergent posterior cranial fossa decompression. The patient subsequently suffered a cardiac arrest and died despite resuscitation attempts. The report is confounded by the patient's underlying neurologic condition and postsurgical complications. The second involved an 8-year-old	The pattern of events evaluated did not show a novel or unusual trend that would suggest a new safety issue. No changes to the CCDS were recommended at that time.

	(gender unknown) with a history of primary pulmonary hypertension who required a surgically inserted intravenous line for further medical therapy. Approximately 60 minutes into the procedure, the patient developed bradycardia with pulseless electrical activity; the patient received cardiac massage and was placed on extracorporeal life support for 5 days. Due to neurological testing that showed a "poor outcome," life support was discontinued, and the patient died at an unspecified time. The report is confounded by the patient's underlying disease (primary pulmonary hypertension), which has a high risk for morbidity and mortality and by multiple concomitant medications. The third report involved a 6-year-old male subject, who underwent excision of a vermian pilocystic astrocytoma. The patient had undergone 3 separate surgeries (isoflurane was used as maintenance anaesthesia for all procedures). He deteriorated neurologically, was intubated and ventilated. Sepsis was suspected. Marked elevations in hepatic enzyme levels and a coagulopathy were noted; followed, over the next 12 hours, by worsening renal function, necessitating haemodialysis, and fulminant hepatic failure. On unknown date, the patient died. An autopsy revealed preserved architecture of zone 1 and severe centrilobular necrosis, "suggestive of drug induced lesion," "in concordance with the changes seen with halothane hepatitis." The last report involved a 10-year-old male subject with eye trauma, who sustained fatal septicaemia, bloody diarrhoea, hematemesis, and disseminated intravascular coagulation. On postoperative Day 1, he developed septicaemia with high fever (41°C) and chills (treated with acetaminophen), bloody diarrhoea and hematemesis. He was diagnosed with disseminated intravascular coagulation and received 1 unit of packed red blood cells,	

	dopamine, and salbutamol nebulizer. The patient died the following day. The case was considered confounded by the history of septicaemia.	

The rapporteur notes that cardiac arrhythmias that can have a fatal outcome and malignant hyperthermia are described as known adverse reactions associated with isoflurane in the current CCDS and UK SmPC of the product. The fatal cases from PSUR 5 appear to be confounded by multiple factors.

The rapporteur acknowledges that the most frequently reported adverse events identified from the aggregate review of PSURs were: malignant hyperthermia, bronchospasm, and cardiac arrest. The current CCDS of isoflurane lists malignant hyperthermia, bronchospasm, respiratory depression as potential serious undesirable effects associated with isoflurane. The CCDS also mentions that *'Cardiac arrest, bradycardia, and tachycardia have been observed with general inhalation anaesthetic drugs including isoflurane.'* The rapporteur therefore concurs with the MAH that the most frequently reported adverse events are consistent with the current CCDS for isoflurane.
The UK SmPC of isoflurane also includes malignant hyperthermia, respiratory depression, bronchospasm, and arrhythmia as most frequent adverse drug reactions. Section 4.8 of the SmPC has the following statement: '*Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period*.'
The above information in the UK SmPC of isoflurane appears to be in line with the CCDS of the product.

The MAH has also reported that an extensive review of reported cases of hyperkalaemic cardiac arrest in infants and children reported in the Malignant Hyperthermia Association of the United States and The North American Malignant Hyperthermia Registry from 1990 – 1993 revealed that potent inhaled anaesthetics (including isoflurane) are associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period.

Based on the submitted data, the rapporteur recommends that the safety information: '*Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period*' should be added in section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects of SmPCs (if not currently included).

Overall, the rapporteur concurs with the MAH that no new safety issues have been identified from the aggregate review of isoflurane PSURs for the period 01 Jan 1993 – 06 Oct 2011.

Effects of anaesthesia on children

The rapporteur notes that the effects of anaesthesia on infants and children were discussed in the March 2011 meeting of the US Food and Drug Administration (FDA) Anaesthetic and Life Support Drugs Advisory Committee. Results of this Advisory meeting have been published (Kuehn BM. FDA considers data on potential risks of anesthesia use in infants, children. JAMA. 2011;305:1749-53). The results are summarised below:

In March 2011, the FDA convened a panel of experts to assess a growing body of evidence from animal studies that suggests anaesthetic agents may harm developing brains, leading to lasting behavioural and cognitive deficits.
For example, one study found that 7-day-old rats exposed to 6 hours of anaesthesia with nitrous oxide, oxygen, isoflurane, and midazolam experienced widespread neurodegeneration and experienced persistent learning deficits (Jevtovic-Todorovic et al, 2003).
However, during the panel meeting, it was also considered that it has been difficult to translate the window of vulnerability from rats to humans because rat brains develop during a relatively short period compared with human brains. To address this challenge, it has been suggested that effects of anaesthetics in young primates, which have a brain development period more similar to that of humans could be explored.
From this panel meeting, the FDA commented that: *"At this time, there is no conclusive evidence that would link exposure to anaesthesia or sedative drugs to neurotoxicity or neurodevelopmental abnormalities. Until additional studies can resolve concerns about the lasting effects of anaesthetic exposure, it would be unethical to have a child undergo a frightening or painful procedure without sedation."* and *"The lack of information to date precludes the ability to designate any one anaesthetic agent or regimen as safer than any other."*
The FDA panel concluded that the evidence is not yet conclusive enough to support warning parents of potential risk, and urged further research.

Rapporteur's comments:
The rapporteur acknowledges that there is emerging concern from animal studies that anaesthetic agents may harm developing brains leading to behavioural or cognitive deficits in juvenile animal models.
The rapporteur notes that Jevtovic-Todorovic et al (2003) demonstrated widespread neurodegeneration and persistent learning deficits in rats treated with a combination of isoflurane and other anaesthetic agents. As isoflurane was used in combination with other agents, the causation of isoflurane cannot be inferred from this study. Furthermore, rats were the animal model used in this study and the FDA panel commented that it has been difficult to translate the window of vulnerability from rats to humans because rat brains develop during a relatively short period compared with human brains.
The rapporteur did not identify any literature articles describing the causative effects of single agent isoflurane on developing brains in animal models.

The rapporteur notes that the FDA concluded that the evidence is not yet conclusive and the FDA did not recommend any changes to product label following the panel meeting.

'A guideline on Summary of Product Characteristics (SmPC) – September 2009' states that: *"If the results of the non-clinical studies do not add to the information needed by the prescriber, then the results (either positive or negative) need not be repeated in the SmPC."*
In line with the SmPC Guideline, the EudraSmPC training presentation on section 5.3. Preclinical safety data recommends that "*the juvenile and relevant peri- or postnatal study results are presented when specific toxicity findings relevant for the paediatric population have been observed. The clinical relevance of the findings should be stated, with a cross-reference to related information in other sections of the SmPC, e.g. section 4.2"*

The rapporteur concludes that sufficient evidence does not exist to make any robust conclusion on the effects of isoflurane on developing brains and changes to section 5.3 Preclinical safety data of the SmPC are not currently warranted.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION AT DAY 89

Based on the data provided as part of this European paediatric work-sharing procedure under Article 45, the rapporteur concludes that the benefit:risk balance of isoflurane remains unchanged for the paediatric population.

The MAH has highlighted paediatric data present in the currently approved UK SmPC and PIL, and the MAH proposes to include this information in all the EU labels.

The rapporteur has reviewed the data submitted as part of this work-sharing procedure and has the following recommendations for all isoflurane SmPCs across the EU:

- To add Minimum Alveolar Concentration (MAC) values of children 0 month – 5 years in section 4.2 Posology and method of administration (supported by submitted clinical study Cameron et al 1984)

- To add the paediatric information on Premedication in section 4.2 Posology and method of administration (supported by submitted clinical study Friesen RH and Lichtor JL 1983)

- To add the paediatric information on laryngospasm in section 4.4 Special warnings and precautions for use (supported by submitted clinical study Friesen RH and Lichtor JL 1983)

- To add the safety information: '*Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period*.' in section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects (supported by submitted aggregate review of PSURs of isoflurane)

Rapporteur's comments:
The MAH also proposes to add the following statement from the UK SmPC to all SmPCs (if not currently included):
Children Under Two Years of Age
Caution should be exercised when isoflurane is used in small children due to limited experience with this patient-group.

The rapporteur considers that this statement is not substantiated by the data submitted as part of this work-sharing procedure.

Based on the data submitted, the MAH should provide the additional clarifications requested per study as part of this work sharing procedure (see section VI "Request for supplementary information")

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

The MAH was requested to submit the following information:

- An overview of all available data evaluating the MAC values of isoflurane in preterm neonates and to consider if the data can support inclusion of MAC values of preterm neonates in the SmPCs.
- An overview of data evaluating MAC values of isoflurane with concomitant administration of nitrous oxide for different paediatric age groups and to consider whether the data are robust enough to add the MAC values of isoflurane in the presence of nitrous oxide to the SmPCs.
- An overview of data evaluating the MAC values of isoflurane in oxygen and isoflurane in oxygen and nitrous oxide in age groups 6-10 years and 10–15 years, in response to one member state's proposal to add these data to the SmPCs.
- A proposal for wording that would be included in the Patient Information Leaflet (PIL) of isoflurane, taking into account the proposed changes to sections 4.2, 4.4 and 4.8 of the SmPC.

VII. MAH RESPONSES TO THE PRELIMINARY PDAR DAY 89

Question 1:
The MAH is requested to submit an overview of all available data evaluating the MAC values of isoflurane in preterm neonates and to consider if the data can support inclusion of MAC values of preterm neonates in the SmPCs.

MAH response:
As noted previously, anesthetic potency for volatile anesthetics is measured in MAC (minimum alveolar concentration) units, with 1 MAC defined as the minimum alveolar concentration that prevents movement in response to surgical stimulation in 50% of subjects. The MAC potency is generally dependent on age.
At the request of the Rapporteur, the MAH has investigated whether further data is available that provide MAC values for pre-term neonates. This investigation revealed no further published literature or available data beyond the previously included study published by LeDez KM and Lerman J entitled "The Minimum Alveolar Concentration (MAC) of Isoflurane in Preterm Neonates" (Anesthesiology, 67:301-307, 1987). This study determined the MAC of isoflurane in two groups of preterm neonates less than 1 month post-natal age who were either <32 weeks or 32-37 weeks gestational age. The MAC (± SD) of isoflurane was significantly less in neonates < 32 weeks gestation, 1.28 ± 0.17% than in neonates 32 – 37 weeks gestation, 1.41 ± 0.18% ($P < 0.05$). Based on this information, the authors conclude that isoflurane is a safe and reliable anesthetic which maintains systolic arterial pressure within the normal range in preterm neonates.
Based on this available data, the MAH proposes that MAC values of isoflurane for preterm neonates be included in the SmPC table reflecting the same, under Section 4.2
Posology and method of administration, as follows:

Age	Average MAC Value In 100% Oxygen	70% N2O
Preterm neonates < 32 weeks gestational age	**1.28%**	
Preterm neonates 32-37 weeks gestational age	**1.41%**	
0-1 month	1.60%	
1-6 months	1.87%	
6-12 months	1.80%	
1-5 years	1.60%	
26 ± 4 years	1.28%	0.56%
44 ± 7 years	1.15%	0.50%
64 ± 5 years	1.05%	0.37%

Rapporteur's comments:
Based on the study published by LeDez KM and Lerman J (previously discussed in section IV.3 of this report), the MAH proposes to add MAC values of isoflurane for preterm neonates < 32 weeks gestational age and preterm neonates 32 – 37 weeks gestational age, in Section 4.2 of the SmPCs. No other additional published literature investigating MAC values in preterm neonates was found by the MAH.
The rapporteur supports the proposed SmPC update in view of the available data from the published study of LeDez KM and Lerman J.
It is noted that the figures in this table corresponding to adult use are not assessed as they are not within the remit of the European paediatric work-sharing procedure under Article 45. As a result, the rapporteur does not propose changes or addition to the adult wording, already included in the nationally authorised SmPCs.

Question 2:
The MAH is requested to submit an overview of data evaluating MAC values of isoflurane with concomitant administration of nitrous oxide for different paediatric age groups and to consider whether the data are robust enough to add the MAC values of isoflurane in the presence of nitrous oxide to the SmPCs.

MAH response:
At the request of the Rapporteur, the MAH has investigated whether additional data is available that provide MAC values with concomitant administration of nitrous oxide in different paediatric age groups. This investigation revealed no further published literature or available data beyond the previously included study published by Murray et al entitled "The Additive Contribution of Nitrous Oxide to Isoflurane MAC in Infants and Children" (Anesthesiology 75:186-190, 1991). This study noted the contribution of nitrous oxide to the MAC of paediatric patients with mean age 16.6 ± 6.7 months, in end tidal concentrations of 0%, 25%, 50%, and 75%) as noted in the following table adapted from Table 1 in the publication:

N_2O (%)	Isoflurane MAC (vol%)
0 (n=11)	1.69 ± 0.13
25 (n=12)	1.26 ± 0.10
50 (n=12)	0.97 ± 0.10
75 (n=12)	0.58 ± 0.09

The purpose of the paper was to determine the contribution of N_2O to isoflurane MAC in paediatric patients; however, no specific age groups were identified. The age range was 7 – 30 months (mean ages 16.6 + 6.7 months). The small number of subjects in each arm does not provide enough statistically significant information (particularly since 70% N_2O was not administered) to provide additional information to the SmPC. The clear summary of the study was that by increasing nitrous oxide concentrations, isoflurane concentrations decreased required for MAC. Additionally MAC values for isoflurane noted in this paper are at a N_2O concentration of 75%. In contrast, the currently approved SmPC states MAC values for N_2O concentration of 70%, rather than 75%, in adult patients greater than age 26. For both these reasons, the MAH considers that the evidence is insufficiently robust to include MAC values for isoflurane in 70% N_2O concentration in the current SmPC.

Rapporteur's comments:
Other than the study published by Murray et al, the MAH did not identify additional data investigating MAC values with concomitant administration of nitrous oxide in different paediatric age groups. The MAH considered that the available evidence is insufficiently robust to include MAC values of paediatric patients for isoflurane in 70% N_2O concentration in the SmPC. The rapporteur concurs with the MAH and the response is accepted.

Question 3:
The MAH is requested to submit an overview of data evaluating the MAC values of isoflurane in oxygen and isoflurane in oxygen and nitrous oxide in age groups 6-10 years and 10–15 years, in response to one member state's proposal to add these data to the SmPCs.

MAH response:
At the request of the Rapporteur, the MAH has investigated whether additional data is available that provide MAC values of isoflurane in oxygen and isoflurane in oxygen and nitrous oxide in age groups 6-10 years and 10–15 years. This investigation revealed no further published literature or available data beyond the previously included reference published by Lopez-Gil M., et al entitled "Safety and efficacy of the laryngeal mask airway: A prospective survey of 1400 children" (Anaesthesia, 1996, Volume 51, pages 969-972). This article describes a survey of laryngeal mask airway usage in 1400 infants and children to provide information about insertion and complication rates using the standard insertion technique for laryngeal mask airway (LMA). In this survey, anesthesia was maintained with either isoflurane or intravenous propofol. The authors concluded that the laryngeal mask provided a safe and effective form of airway management for infants and children in the hands of supervised anesthesia trainees using either isoflurane or total intravenous anesthesia. Goal of this study was not focused on MAC values, but more on the use of the LMA and subsequent problems identified with its use in the pediatric population. The safety and efficacy of isoflurane was not further discussed. Based on this

information, the MAH considers that the evidence is insufficient to include MAC values of isoflurane in age groups 6-10 years and 10-15 years.

Rapporteur's comments:
The rapporteur agrees with the MAH that the published survey by Lopez-Gil M et al was not focussed on safety and efficacy of isoflurane and/or MAC values. The MAH did not identify additional data focussing on MAC values in children aged 6-10 years and 10-15 years and considered that there is insufficient evidence to include MAC values for these age groups. The rapporteur considers the MAH response acceptable.

ADDITIONAL REQUEST FOR CLARIFICATION ON PROPOSED SmPC WORDING

The rapporteur also requested the MAH to clarify the addition of the statement '*Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period.'* in section 4.8 of the SmPC, under the heading 'Neuromuscular disease'.

MAH response:
On Nov. 15, 2005, the MAH received correspondence from the FDA directed to the Ultane® (Sevoflurane) licence requesting that the labelling of Sevoflurane be changed to reflect rare post-marketing reports of hyperkalemia, cardiac arrhythmias, and hepatic failure associated with inhaled anaesthetic agents, including Sevoflurane. Based on the available reports, the MAH believed there is potential of these adverse effects occurring with any potent inhaled volatile anaesthetic agent, including isoflurane. Thus, the MAH amended their core data sheet for isoflurane to reflect this potential risk and subsequently obtained approval in the EU via a labelling variation.
The MAH also submitted the FDA request and the published paper on which the FDA request was based as supportive data for the inclusion of the above statement under "neuromuscular disease" in all the EU SmPCs.

Rapporteur's comments:
The MAH submitted a paper entitled 'Hyperkalaemic cardiac arrest during anesthesia in infants and children with occult myopathies' by Larach et al (1997).
In this study, using data from 1990 to 1993, the authors analysed all reports of paediatric arrests occurring in 24 hours of anesthesia. Aetiology of arrests and presence of myopathy were determined. There were reports of twenty-five patients who arrested. A previously unrecognised Duchenne dystrophy (n=8) or unspecified myopathy (n=4) was diagnosed in 12 (48%) patients. Eight of these 12 patients' arrests were associated with hyperkalemia. Ten (40%) patients had no postarrest evaluation to exclude occult myopathy.
The authors reported that anaesthetics triggering the arrests included potent inhalational agents with or without succinylcholine. The authors concluded that, whenever possible, paediatricians should evaluate their patients (especially male infants and children) preoperatively for the presence of occult myopathy.

Based on the FDA request and the published paper described above, the MAH believed that these adverse effects could potentially occur with any inhaled volatile anaesthetic agent and therefore, the MAH amended their core clinical data sheet for isoflurane to reflect this potential risk.

The rapporteur notes that the currently approved FDA label of isoflurane and the currently approved UK SmPC of isoflurane contain the following warning:

Perioperative Hyperkalaemia

Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period. Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable. Concomitant use of succinylcholine has been associated with most, but not all, of these cases. These patients also experienced significant elevations in serum creatine kinase levels and, in some cases, changes in urine consistent with myoglobinuria. Despite the similarity in presentation to malignant hyperthermia, none of these patients exhibited signs or symptoms of muscle rigidity or hypermetabolic state. Early and aggressive intervention to treat the hyperkalaemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease.

The currently approved UK SmPC of isoflurane also contains the following information in Section 4.8:

Section 4.8 Undesirable effects

e. Other special populations

Neuromuscular disease:

Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period. Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable. (See 4.4)

The rapporteur notes that although the published paper reported that the arrests occurred with use of potent inhalational agents, the inhalational agents used in the arrest cases were not specified. However, the rapporteur agrees with the applicant that the potential risk may also apply to the inhaled anaesthetic agent isoflurane.

The labelling changes to the UK SmPC of isoflurane related to the addition of the above information on hyperkalaemia were implemented in 2007.

Based on the submitted information regarding this potential risk, the rapporteur recommends that the SmPCs of all products containing isoflurane across the EU contain the following statements (if not already included):

Section 4.4 Special warnings and precautions for use

<u>Perioperative hyperkalaemia</u>

Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period. Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable. Concomitant use of succinylcholine has been associated with most, but not all, of these cases. These patients also experienced significant elevations in serum creatine kinase levels and, in some cases, changes in urine consistent with myoglobinuria. Despite the similarity in presentation to malignant hyperthermia, none of these patients exhibited signs or symptoms of muscle rigidity or hypermetabolic state. Early and aggressive intervention to treat the hyperkalaemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease.

Section 4.8 Undesirable effects
Other special populations
Neuromuscular disease:
Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period. Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable. Early and aggressive intervention to treat the hyperkalaemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease (see section 4.4).

Question 4:
The MAH is requested to submit a proposal for wording that would be included in the Patient Information Leaflet (PIL) of isoflurane, taking into account the proposed changes to sections 4.2, 4.4 and 4.8 of the SmPC.

MAH response:
As part of this Art 45 submission the MAH proposes the inclusion of the currently approved pediatric wording from the UK SmPC and Patient Information Leaflet (PIL) in all the currently registered EU SmPCs and PILs.

Rapporteur's comments:
Based on the review of the submitted data as part of this work-sharing procedure, the rapporteur is making recommendations for important paediatric information to be added (if not already included) in corresponding sections of the SmPC/PIL for all isoflurane products.
The final SmPC and PIL wording are presented in section IX Rapporteur's final conclusion and recommendation.

1. **PIL change**

The MAH proposes inclusion of Children in Section 4 of the PIL (**bold** & underline) as follows:

4. What will happen after receiving Isoflurane?
"If you **or your child** *suffer from any unusual or unexpected symptoms after ~~your~~* ***an*** *operation tell your doctor or anaesthetist* ***IMMEDIATELY."***

Rapporteur's comments:
The proposed wording for this PIL update is accepted.

In red is the currently approved wording in the UK SmPC and in **bold** & underline is the new proposed wording (for inclusion in the SmPC and PIL):

2. **PIL change**

SmPC 4.2 Posology and method of administration:
MAC values for isoflurane vary with age. The table below indicates average MAC values for different age groups.

Age	Average MAC Value In 100% Oxygen
Preterm neonates < 32 weeks gestational age	**1.28%**
Preterm neonates 32-37 weeks gestational age	**1.41%**
0-1 month	1.60%
1-6 months	1.87%
6-12 months	1.80%
1-5 years	1.60%

PIL update:
The MAC values included within the table are for health care professional (HCP) administrating the product. In the MAH's opinion any terminology included in the PIL related to MAC values would be complicated and not patient friendly, hence the following existing wording should be sufficient in relation to "posology and method of administration" for the PIL:

3. How will you receive Isoflurane?
*"Isoflurane will **ALWAYS** be administered to you by an anaesthetist. They will decide on the dose you will receive, depending on your age, weight and the type of operation you are having"*

Rapporteur's comments:
The proposed wording for this PIL update is accepted.

3. PIL change

SmPC 4.2 Posology and method of administration:

Premedication: Drugs used for premedication should be selected for the individual patient bearing in mind the respiratory depressant effect of isoflurane. The use of anticholinergic drugs is a matter of choice, but may be advisable for inhalation induction in paediatrics.

PIL update:
The MAH proposes the following statement related to Premedication drugs:

3. How will you receive Isoflurane?
Inducing sleep at the start of anaesthesia
"Very occasionally you may be asked to breathe in the Isoflurane via a mask. **Anaesthetist may decide to give your child medication to counter act the possible reduction in breathing and heart rate effects which may occur with the use of Isoflurane.** *Usually you will receive an injection of another anaesthetic to make you go to sleep before you receive Isoflurane.*

Rapporteur's comments:
The proposed wording regarding premedication drugs for the PIL is accepted. However, the rapporteur proposes to have this wording under the sub-heading: 'Medication before anaesthesia'.

⇩

Medication before anaesthesia
Anaesthetist may decide to give your child medication to counter act the possible reduction in breathing and heart rate effects which may occur with the use of Isoflurane.

4. **PIL change**

SmPC 4.4 Special warnings and precautions for use:
During the induction of anaesthesia, saliva flow and tracheobronchial secretion can increase and can be the cause of laryngospasm, particularly in children.

PIL update:
In the MAH's opinion, the existing wording (see below) in Section 4 of the PIL covers the warning related to "Laryngospasm"

4. What will happen after receiving Isoflurane?
"A tightening of your lungs and airways causing a difficulty in breathing"

Rapporteur's comments:
The existing wording relating to 'Laryngospasm' in the PIL is accepted.

5. **PIL change**

SmPC 4.4 Special warnings and precautions for use:

Children Under Two Years of Age
Caution should be exercised when isoflurane is used in small children due to limited experience with this patient-group.

PIL update:
MAH propose the following wording to cover the warning related to the use of the product in small children due to the limited experience with this patient-group.

3. How will you receive Isoflurane?
"Your child should be monitored closely during the administration of Isoflurane"

Rapporteur's comments:
The MAH proposes to add the following statement from the UK SmPC to all SmPCs (if not currently included):

Children Under Two Years of Age

Caution should be exercised when isoflurane is used in small children due to limited experience with this patient-group.

As the statement is already included in the UK SmPC, the corresponding update to the UK PIL is accepted.
However, it is to be noted that the data submitted as part of this work-sharing procedure do not support the addition of this statement to all SmPCs and therefore the PIL update cannot be substantiated if this statement is lacking in the SmPC.

6. PIL change

SmPC 4.4 Special warnings and precautions for use:

Perioperative Hyperkalaemia
Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in pediatric patients during the post-operative period. Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable. Concomitant use of succinylcholine has been associated with most, but not all, of these cases. These patients also experienced significant elevations in serum creatine kinase levels and, in some cases, changes in urine consistent with myoglobinuria. Despite the similarity in presentation to malignant hyperthermia, none of these patients exhibited signs or symptoms of muscle rigidity or hypermetabolic state. Early and aggressive intervention to treat the hyperkalaemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease.

MAH propose the following wording in Section 4 to cover the warning related to "increases in serum potassium levels and resulting cardiac arrhythmias"

4. What will happen after receiving Isoflurane?
"Increases in blood sugar levels or potassium levels", **there have been reports of abnormal heartbeat (arrhythmias) and death associated with the use of inhaled anaesthetics in children shortly after surgery**

Rapporteur's comments:
Prior to finalisation of this work-sharing procedure, the rapporteur and MAH agreed on a minor change to the above PIL wording to better reflect the information in the SmPC.
The final PIL wording agreed upon is:

Section 4. What will happen after receiving Isoflurane?
"Increases in blood sugar levels or potassium levels. **There have been rare reports of abnormal heartbeat (arrhythmias) and death associated with the use of inhaled anaesthetics in children shortly after surgery.**"

7. PIL change

SmPC 4.8 Undesirable effects:

d. Paediatric population
Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period. (See 4.4.)

e. Other special populations
Neuromuscular disease
Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period. Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable. (See 4.4.)

PIL update:
MAH propose the following wording in Section 4 to cover the warning related to "increases in serum potassium levels and resulting cardiac arrhythmias"

4. What will happen after receiving Isoflurane?
"Increases in blood sugar levels or potassium levels", **there have been reports of abnormal heartbeat (arrhythmias) and death associated with the use of inhaled anaesthetics in children shortly after surgery**

Rapporteur's comments:
Per the previous rapporteur's comment, the final PIL wording agreed upon by the rapporteur and MAH is:
"Increases in blood sugar levels or potassium levels. **There have been rare reports of abnormal heartbeat (arrhythmias) and death associated with the use of inhaled anaesthetics in children shortly after surgery.**"

VIII. REVIEW OF 'THE USE OF ISOFLURANE FOR INDUCTION OF ANAESTHESIA IN CHILDREN'

- One member state sent comments questioning the use of isoflurane for induction of anaesthesia in children and requested reflection in this clinical context.

  The member state sought the advice of the European Society for Paediatric Anaesthesiology (ESPA).

- The ESPA statement is provided below:

  Isoflurane for use in infants and children

  Isoflurane is a methyl ethyl ether anesthetic that was introduced about 1979. At that time, isoflurane offered advantages over the more soluble anesthetic, halothane, in terms of recovery. However, numerous studies demonstrated that a mask induction of anesthesia with isoflurane was challenging because the frequencies of laryngospasm, breath-holding, coughing, desaturation and movement were substantial and quite worrisome. At that time, there were no mandated federal requirements that pharmaceutical companies investigate the effects of new anesthetics in infants and children. As a consequence, isoflurane was released into the market with supporting documentation from studies in adults, without a pediatric indication or warning, leaving investigators to study the effects of isoflurane on induction of anesthesia in children post--release.

  A number of studies were published in which isoflurane was used to induce anesthesia in infants and children. These studies included comparators such as enflurane, halothane and/or sevoflurane. In most studies, the frequencies of airway reflex responses including coughing, breath-holding, laryngospasm and desaturation as well as movement after isoflurane were greater than those after the comparators (except for enflurane in some studies). Some clinicians investigated interventions to attenuate the frequency of these responses and concluded that premedicating the children or administering an intravenous induction agent first attenuated, but did not totally eliminate the airway reflex responses. The net conclusion in the pediatric anesthesia community has been that methyl ethyl ether anesthetics such as isoflurane are neither suitable nor appropriate for induction of anesthesia in infants and children. The specific risks of laryngospasm and oxygen desaturation rendered isoflurane a less-than-suitable anesthetic for induction of anesthesia. Parenthetically, at the time isoflurane was introduced into the market, no federal licensing body anywhere in the world that I am aware of, mandated testing of these new anesthetics in infants and children before the drug was approved. Hence, properly conducted studies regarding the suitability of isoflurane for induction of anesthesia in infants and children were never performed.

  In contrast, desflurane, a stereoisomer of isoflurane, was introduced into practice in the early 1990's, at a time when federal agencies mandated pediatric trials. These latter studies clearly identified serious adverse airway events when concentrations of desflurane in excess of 5% inspired were administered to children, which led to a warning in the package insert that this anesthetic is NOT suitable for induction of anesthesia in infants and children. In contrast, sevoflurane, a methyl isopropyl ether anesthetic, rarely triggers airway reflex responses and is specifically indicated and designated for induction of anesthesia in infants and children by the federal authorities in most countries. This has led to sevoflurane becoming the standard of care for inhalational inductions in infants and children.

  Isoflurane has been used for decades for maintenance of anesthesia in infants and children. Once anesthesia is induced and a deep level of anesthesia achieved, isoflurane is reasonably well-tolerated. This is particularly true once the trachea has been intubated. The same holds true for desflurane. Recent evidence however, has suggested that there is a

greater incidence of upper airway reflex responses with these agents when a supraglottic airway is used compared with propofol, although serious adverse events were infrequent. It appears that the inherent risks of airway reflex responses are greater with both isoflurane and desflurane when the airway is not instrumented with an endotracheal tube compared with sevoflurane. A greater skill level is required by the practitioner to ensure the depth of anesthesia is sufficient with both isoflurane and desflurane to preclude airway reflex responses with either no instrumentation of the airway or a supraglottic device compared with that of sevoflurane.

In conclusion, I caution against recommending or condoning induction of anesthesia with isoflurane by mask in infants and children. Although isoflurane has been used for induction of anesthesia by a number of skilled practitioners, it is a much less robust anesthetic than sevoflurane, presenting a much greater risk of laryngospasm and desaturation than sevoflurane, especially in inexperienced hands. Therefore, the risks of anesthesia in the infant and child would be substantially reduced if the labeling for isoflurane unambiguously warned against its use for induction of anesthesia by mask in infants and children.

The rapporteur sought the opinion of the Association of Anaesthetists of Great Britain and Ireland in relation to the current clinical use of isoflurane for induction of anaesthesia in children.

- **Opinion of the Association of Anaesthetists of Great Britain and Ireland**

  "The details that are proposed to be included in the report concur with current practice in the UK. Isoflurane may be used during maintenance but it is not used as an agent for gaseous induction in children (not generally for adults) because of irritant effects. Sevoflurane is the preferred inhalational anaesthetic for gaseous inductions in children. Isoflurane may serve an alternative to sevoflurane."

Furthermore, the rapporteur reviewed the adverse event data associated with isoflurane from the UK yellow card scheme to gain an understanding of reported adverse events in children.

- **UK Spontaneous suspected adverse drug reactions reported with isoflurane in the paediatric population**

During the period 01/07/1963 until 03/03/2015, there have been a total of 146 reactions associated with isoflurane in paediatric patients 0 – 18 years, reported to the UK yellow card scheme.

The number of reactions per MedDRA SOC (Medical Dictionary for Regulatory Activities System Organ Class) is shown in the table below:

MedDRA SOC	Number of reactions for children 0 to 18 years	Fatal
Cardiac disorders	7	0
Eye disorders	1	0
Gastrointestinal disorders	1	0
General disorders	8	0
Hepatic disorders	1	0
Injuries	23	0
Investigations	9	0
Metabolic disorders	7	0
Muscle and tissue disorders	5	0
Nervous system disorders	21	1
Pregnancy conditions	3	0
Psychiatric disorders	41	0
Renal and urinary disorders	2	0
Respiratory disorders	6	0
Skin disorders	1	0
Surgical and medical procedures	7	0
Vascular disorders	3	0
TOTAL	**146**	**1**

The reactions in the Respiratory disorders SOC are further broken down below:

Reaction name	Total	Fatal
Respiratory arrest	1	0
Obstructive airways disorder	1	0
Hypoxia	2	0
Respiratory acidosis	1	0
Pulmonary hypertension	1	0
Respiratory disorders SOC TOTAL	**6**	**0**

Rapporteur's comments:
Data obtained from the UK yellow card scheme indicate that out of a total of 146 reactions associated with isoflurane in children, 6 belonged to the respiratory disorders SOC (for the period 01/07/1963 - 03/03/2015). None of these 6 reactions were fatal. The rapporteur recognises that reporting of spontaneous adverse reactions is influenced by many factors and under-reporting of suspected adverse reactions associated with isoflurane cannot be excluded.

During this work-sharing procedure, one member state has highlighted that in clinical practice, induction of anaesthesia with isoflurane via mask is obsolete due to its pungent odour, stimulation of secretions and airway irritating properties possibly leading to laryngospasm. In this regard, the ESPA and AAGBI have given opinions that isoflurane is not considered an appropriate induction agent in children because of its airway reflex responses including

coughing, breath-holding, laryngospasm and desaturation. Both expert groups have also reported that isoflurane may be used for maintenance of anaesthesia in children and have stated that in clinical practice, sevoflurane is the preferred inhalational anaesthetic agent in paediatrics. This was also reflected in the available literature and clinical guidelines reviewed by the rapporteur.

Based on the submitted information, the rapporteur concludes that there is evidence that isoflurane has significant airway irritating properties when used as an induction agent in children. Two anaesthetic expert groups have confirmed that isoflurane is not considered an appropriate anaesthetic agent for induction of anaesthesia in children due to these safety risks and its use in this clinical context has been superseded by alternative agents that appear to be safer alternatives. Therefore, the rapporteur proposes to include wording in section 4.2 of the SmPCs of all isoflurane containing products to indicate that the use of isoflurane is not recommended for induction of anaesthesia in children in line with current clinical practice. This wording will be cross-referenced to the warning on laryngospasm in section 4.4.

The following wording and cross-reference are proposed:

Section 4.2 Posology and method of administration
Induction of anaesthesia in children:
Isoflurane is not recommended for use as an inhalation induction agent in infants and children because of the occurrence of cough, breath-holding, desaturation, increased secretions and laryngospasm (see section 4.4).

Section 4.4 Special warnings and precautions for use
During the induction of anaesthesia, saliva flow and tracheobronchial secretion can increase and can be the cause of laryngospasm, particularly in children.

For the PIL, the rapporteur proposes the below wording:

Section 3 - How will you receive Isoflurane?

Inducing sleep at the start of anaesthesia
Isoflurane is not recommended in infants and children for inducing sleep at the start of anaesthesia.

IX. RAPPORTEUR'S FINAL CONCLUSION AND RECOMMENDATION

Taking into account the submitted data package, comments received from member states and the advice received from the anaesthetic expert groups, the rapporteur concludes that the following changes in SmPC and PIL are recommended for all isoflurane containing products:

SUMMARY OF PRODUCT CHARACTERISTICS

Section 4.2 Posology and method of administration

[This section should be amended to include the below wording]

[…]

ADULTS*		
Age	**Average MAC Value In 100% Oxygen**	**70% N_2O**
26 ± 4 years	1.28%	0.56%
44 ± 7 years	1.15%	0.50%
64 ± 5 years	1.05%	0.37%

PAEDIATRIC POPULATION	
Age	**Average MAC Value In 100% Oxygen**
Preterm neonates < 32 weeks gestational age	1.28%
Preterm neonates 32-37 weeks gestational age	1.41%
0-1 month	1.60%
1-6 months	1.87%
6-12 months	1.80%
1-5 years	1.60%

Premedication: Drugs used for premedication should be selected for the individual patient bearing in mind the respiratory depressant effect of isoflurane. The use of anticholinergic drugs is a matter of choice, but may be advisable for inhalation induction in paediatrics.

Induction of anaesthesia in children:
Isoflurane is not recommended for use as an inhalation induction agent in infants and children because of the occurrence of cough, breath-holding, desaturation, increased secretions and laryngospasm (see section 4.4).

*[*Rapporteur's comment: The information in the table corresponding to adult use should remain unchanged as currently approved in SmPCs as it is outside the remit of this European Paediatric work-sharing procedure under Article 45. Additionally, according to the European Commission A guideline on SmPC (September 2009), "each section of the SmPC should first deal with those issues that apply to the core population for whom the medicine is indicated followed - when necessary – by specific information for any relevant special population (e.g. children)." Therefore, the MAC values for adults appear at the top of the table, followed by the MAC values for children under the sub-heading 'PAEDIATRIC POPULATION'.]*

Section 4.4 Special warnings and precautions for use

[This section should be amended to include the below wording]

During the induction of anaesthesia, saliva flow and tracheobronchial secretion can increase and can be the cause of laryngospasm, particularly in children.

Perioperative Hyperkalaemia
Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period. Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable. Concomitant use of succinylcholine has been associated with most, but not all, of these cases. These patients also experienced significant elevations in serum creatine kinase levels and, in some cases, changes in urine consistent with myoglobinuria. Despite the similarity in presentation to malignant hyperthermia, none of these patients exhibited signs or symptoms of muscle rigidity or hypermetabolic state. Early and aggressive intervention to treat the hyperkalaemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease.

Section 4.8 Undesirable effects

[This section should be amended to include the below wording]

Paediatric population
Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period (see section 4.4).

Other special populations
Neuromuscular disease:
Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period. Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable. Early and aggressive intervention to treat the hyperkalaemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease (see section 4.4).

PACKAGE INFORMATION LEAFLET

Section 3 - How will you receive Isoflurane?

[This section should be amended to include the below wording]

Isoflurane will ALWAYS be administered to you by an anaesthetist. They will decide on the dose you will receive, depending on your age, weight and the type of operation you are having.

Your child should be monitored closely during the administration of Isoflurane *[Rapporteur's comment: This statement may be added if the corresponding paediatric statement is already included in the SmPC]*

Inducing sleep at the start of anaesthesia
Isoflurane is not recommended in infants and children for inducing sleep at the start of anaesthesia.

Medication before anaesthesia
Anaesthetist may decide to give your child medication to counter act the possible reduction in breathing and heart rate effects which may occur with the use of Isoflurane.

Section 4 - What will happen after receiving Isoflurane?

[This section should be amended to include the below wording]

If you or your child suffer from any unusual or unexpected symptoms after an operation tell your doctor or anaesthetist IMMEDIATELY.

The most commonly reported side effects are:

- A tightening of your lungs and airways causing a difficulty in breathing
- Increases in blood sugar levels or potassium levels. There have been rare reports of abnormal heartbeat (arrhythmias) and death associated with the use of inhaled anaesthetics in children shortly after surgery

---

The applicant is therefore requested to submit a Type IB variation to update the SmPCs and PILs of isoflurane containing products in line with the above work-sharing recommendations within 60 days of this report.

X. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

MAH	MEDICINAL PRODUCT
Abbott	Isoflurane 99.9 % w/w (FORANE)

XI. ADDITIONAL REFERENCES FROM RAPPORTEUR

A guideline on Summary of Product Characteristics (SmPC) – September 2009 by the European Commission.
Available from:
http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf
[Viewed 23 July 2014]

EU SmPC training presentation on Section 5.3 Preclinical safety data.
Available from:
http://eudrasmpc.eudra.org/trainingpresentations/5.3%20Preclinical%20Safety%20Data%20Presentation.pdf
[Viewed 23 July 2014]

Jevtovic-Todorovic V, Hartman RE, Izumi Y, et al. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. J Neurosci 2003;23:876–82

Kuehn BM. FDA considers data on potential risks of anesthesia use in infants, children. JAMA. 2011;305:1749-53

Larach,MG. Hyperkalemic cardiac arrest during anesthesia in infants and children with occult myopathies. Clinical Pediatrics 1997;36(1):9-16.

Recommendations on submission & assessment in paediatric worksharing by The Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh).
Available from:
http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Paediatric_Regulation/Guidance_Documents/Art_45/CMDh_141_2009_Rev2_Clean.pdf
[Viewed 23 July 2014]