1.0 TITLE PAGE

Application for Inclusion of Sevoflurane on the WHO Model List of Essential Medicines (EML)

Contact Information

Bhadrish Vallabh, MD, MBA, M Fam Med
AbbVie Biopharmaceuticals GmbH
Floor 29, Office 2901, UBORA Tower,
Business Bay, P.O. Box 118052 Dubai
United Arab Emirates
OFFICE: +9714 550 6100
FAX: +9714 550 6199
DIRECT: +9714 550 6192
MOBILE: +9715 02404285
EMAIL bhadrish.vallabh@abbvie.com

2.0 SUMMARY STATEMENT OF THE PROPOSAL FOR INCLUSION, CHANGE OR DELETION

Sevoflurane is being proposed for inclusion on the core WHO Model List of Essential Medicines (EML) as an option for an inhalational gas under anesthetics, preoperative medicines, and medical gases for the treatment of adult and pediatric patients.

Since its first market authorization on 23 January 1990 in Japan, sevoflurane has achieved regulatory approvals in at least 113 countries (see detailed list for AbbVie approvals in Section 12.0) for its use as an anesthetic agent in a variety of patient populations. Due to this wide accessibility, it was estimated that more than 1,000,000,000 patients have been exposed to this product.[1] It is important to note that this exposure number is strictly associated with sevoflurane marketed by Abbvie and Maruishi, and does not include sevoflurane products from other manufacturers, for example Baxter and Piramal Pharma (other large-scale producers). The fact that there are multiple manufacturers for sevoflurane around the world also supports the position that patient access is widely available and stable supply chains are established - an essential precondition for this request. This broad utilization is also an indicator that sevoflurane's pharmacology and its positive benefit-risk ratio is well understood and clinically appreciated by anesthesiologists worldwide.

Presently, there are only two volatile inhalational anesthetic agents, halothane and isoflurane, included in the EML. Since halothane is often contraindicated and was taken off the market in certain countries, the question arises whether an important alternative should be considered, namely sevoflurane. Besides its broad accessibility and clinical benefits, one of the key factors for this request is found in environmental considerations.

Climate change has become a top-line agenda item, particularly in recent years, in both developed and developing countries. All sectors of the economy are expected to contribute by finding ways to reduce emission of harmful gases (inhalational anesthetic agents) and decrease overall energy use. Inhaled anesthetics contribute to climate change but their impact could be

greatly reduced by ending the use of the most significant contributors and reducing the use of those that are less impactful to the environment.

Although all volatile anesthetics (e.g., sevoflurane, desflurane, isoflurane) must be considered as greenhouse gases, the level of impact with their specific global warming potential (GWP) differs significantly. For example, sevoflurane has a GWP of 440, whereas isoflurane and desflurane have GWPs of 1800 and 6810 respectively.[2] This means that isoflurane and desflurane have environmental impacts of 4.09 and 15.48 times greater when compared to sevoflurane. Sevoflurane, isoflurane, and desflurane have atmospheric lifetimes of 1.1, 3.2, and 14 years, respectively.[2] Nitrous oxide is another gaseous agent used for anesthesia, and although it has a GWP of only 289, it has an atmospheric lifetime of 120 years[3] and therefore should be used judiciously by the clinician. It is for these reasons that several organizations demand changes in the way these gases are used. For example, the European Society of Anaesthesiology and Intensive Care (ESAIC) issued a position statement[4] in June 2022 with the following content:

Results of the evidence as suggested by a statement from ESAIC (June 2022): “There are several ways to reduce emissions, which include ending the use of nitrous oxide, desflurane and isoflurane immediately, though a combination of efficient use of the only other available alternative (sevoflurane), and switching to other modes of anesthesia such as TIVA (total intravenous anesthesia) and regional anesthesia (spinal/epidural/nerve blocks); and also capturing volatile anesthetics from the exhaust air piping”. Since a complete ban on desflurane is now being prepared by the European Commission,[5] which will come into effect on 1 January 2026, this proposal will highlight the clinical usefulness of sevoflurane in a changing environment. A specific example included in the statement mentioned how Amsterdam University Medical Center reduced emissions by eliminating desflurane, isoflurane, and nitrous oxide but continuing to use sevoflurane albeit at about 30% of previous use.

Based on these developments and the fact that sevoflurane is already broadly used on a global basis, we advocate to add this product to WHO’s EML for its use as anesthetic agent in adult and pediatric patients in accordance with its locally registered labels.

3.0 CONSULTATION WITH WHO TECHNICAL DEPARTMENTS

The following person was contacted by one of our team members to discuss our submission:

Benedikt David Huttner
Team Lead EML
Department of Essential Medicines and Health Products
Geneva, Switzerland
Mobile: +41 79 500 65 92
Web: www.who.int

4.0 OTHER ORGANIZATION(S) CONSULTED AND/OR SUPPORTING THE SUBMISSION

The European Society of Anaesthesiology and Intensive Care (ESAIC) released a statement on 3 June 2022 regarding the use of inhaled anesthetics which was reviewed at their yearly meeting. To reduce emissions of these greenhouse gases, it was suggested to end the use of nitrous oxide, desflurane, and isoflurane immediately and to more efficiently use sevoflurane.

The following letters of support for this submission can be found in the appendices.

Professor Matthieu Jabaudon, MD, PhD

Professor PD Gopalan, MBChB, FCA, PhD

The South African Society of Anaesthesiologists

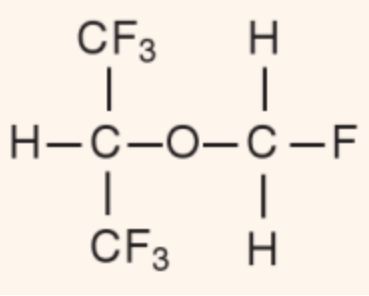
Professor Khaled Yassen

5.0 KEY INFORMATION FOR THE PROPOSED MEDICINE(S)

5.1 International non-proprietary name (INN) and anatomical therapeutic chemical (ATC) code of the medicine.

INN: sevoflurane

fluoromethyl 2,2,2,-trifluoro-1-(trifluoromethyl) ethyl ether



5.2 ATC code: N01AB08 (sevoflurane)

5.3 Dosage form and strength of the proposed medicine

The concentration of sevoflurane being delivered from a vaporizer should be known. This may be accomplished by using a vaporizer calibrated specifically for sevoflurane. The administration of general anesthesia must be individualized based on the patient's response.

5.3.1 Replacement of desiccated CO_2 absorbents

When a clinician suspects that the CO_2 absorbent may be desiccated, it should be replaced. The exothermic reaction that occurs with sevoflurane and CO_2 absorbents is increased when the CO_2 absorbent becomes desiccated, such as after an extended period of dry gas flow through the CO_2 absorbent canisters (see **PRECAUTIONS** in Ultane [sevoflurane] United States Prescribing Information [USPI][6]).

5.3.2 Pre-anesthetic medication

No specific premedication is either indicated or contraindicated with sevoflurane. The decision as to whether to premedicate and the choice of premedication is left to the discretion of the anesthesiologist.

5.3.3 Induction

Sevoflurane has a non-pungent odor and does not cause respiratory irritability; it is suitable for mask induction in pediatrics and adults.

5.3.4 Maintenance

Surgical levels of anesthesia can usually be achieved with concentrations of 0.5 – 3% sevoflurane with or without the concomitant use of nitrous oxide. Sevoflurane can be administered with any type of anesthesia circuit.

The minimum alveolar concentration (MAC) values for adults and pediatric patients by age is shown in Table 1.

Table 1. MAC Values for Adults and Pediatric Patients According to Age

Age of Patients (years)	Sevoflurane in Oxygen	Sevoflurane in 65% N_2O/35% O_2
0 – 1 months[a]	3.3%	
1 – < 6 months	3.0%	
6 months – < 3 years	2.8%	2.0%[b]
3 – 12	2.5%	
25	2.6%	1.4%
40	2.1%	1.1%
60	1.7%	0.9%
80	1.4%	0.7%

Source: Sevoflurane US FDA PI.[6]
[a]Neonates are full-term gestational age. MAC in premature infants has not been determined.
[b]In 1 – < 3 year old pediatric patients, 60% N_2O/40% O_2 was used.
Abbreviation: MAC = minimum alveolar concentration

5.4 Indication

Sevoflurane is indicated for induction and maintenance of general anesthesia in adult and pediatric patients for inpatient and outpatient surgery.

Sevoflurane should be administered only by persons trained in the administration of general anesthesia. Facilities for maintenance of a patent airway, artificial ventilation, oxygen enrichment, and circulatory resuscitation must be immediately available. Since level of anesthesia may be altered rapidly, only vaporizers producing predictable concentrations of sevoflurane should be used.

6.0 PROPOSAL FOR AN INDIVIDUAL MEDICINE OR REPRESENTATIVE OF A PHARMACOLOGICAL CLASS / THERAPEUTIC GROUP.

The Essential Medicines Listing for sevoflurane is being requested as an individual essential medicine within the class of inhalational anesthetics used for general anesthesia before and during surgery.

7.0 INFORMATION SUPPORTING THE PUBLIC HEALTH RELEVANCE

7.1 Epidemiological information on disease burden

Globally, approximately 6% of the world's population requires surgery and that anesthesia will be required for about 92% of the surgeries.[7] These estimates are from 2016, so the percentages may differ from the time of this submission in 2022. The overarching goal of anesthesia is to block sensation either to a specific area or the whole body. In general anesthesia, the patient is kept in a safe and controlled state of unconsciousness by a mixture of drugs and sensation is blocked to the entire body. In 2008, the WHO estimated that there were about 234 million major surgical procedures worldwide every year[8] but is likely higher than that in 2022. The inhalational anesthetics, sevoflurane in particular, are not only used in major surgeries, but may also be used in outpatient surgeries and dental procedures.

The most commonly used inhalational anesthetics are halothane, sevoflurane, desflurane, isoflurane, and nitrous oxide.[9] Of these, sevoflurane is the most common because of its low blood-gas solubility allowing for rapid induction and quick recovery time, less irritating to the airway passages, lower pungency, and acceptable cardiovascular side effect profile.[10-12]

An estimate of the patient exposure treated with sevoflurane was calculated from AbbVie and co-marketer Maruishi sales data. Using the total number of liters distributed and multiplying by the average treatments per liter, 49.5, an estimate of the number of patient treatments (PTx) was calculated to be 1,194,664,678. This calculation is based on the dates of 01 September 1994 through 31 January 2022.

Sevoflurane is currently approved in at least 113 countries worldwide; however, this includes only approvals for AbbVie so there might be approvals in additional countries by other manufacturers of sevoflurane.

7.2 Target populations

The targeted populations include induction and maintenance of general anesthesia in both adults and pediatric patients for inpatient and outpatient surgery.

7.3 Alternative medicines currently included on the Model Lists for the proposed indication

Inhalation anesthetics currently included on the WHO Model Lists include halothane, isoflurane, and nitrous oxide.

8.0 TREATMENT DETAILS

8.1 Dosage regimen and duration of treatment

Sevoflurane is indicated for induction and maintenance of general anesthesia in adult and pediatric patients for inpatient and outpatient surgery.

8.2 Requirements to ensure appropriate use of the medicine(s)

Sevoflurane should be administered only by persons trained in the administration of general anesthesia. Facilities for maintenance of a patent airway, artificial ventilation, oxygen enrichment, and circulatory resuscitation must be immediately available. Since level of anesthesia may be altered rapidly, only vaporizers producing predictable concentrations of sevoflurane should be used.

An exothermic reaction occurs when sevoflurane is exposed to CO_2 absorbents. This reaction is increased when the CO_2 absorbent becomes desiccated, such as after an extended period of dry gas flow through the CO_2 absorbent canisters. Rare cases of extreme heat, smoke, and/or spontaneous fire in the anesthesia breathing circuit have been reported during sevoflurane use in conjunction with the use of desiccated CO_2 absorbent, specifically those containing potassium hydroxide (e.g., Baralyme). KOH containing CO_2 absorbents are not recommended for use with sevoflurane. An unusually delayed rise or unexpected decline of inspired sevoflurane concentration compared to the vaporizer setting may be associated with excessive heating of the CO_2 absorbent and chemical breakdown of sevoflurane.

As with other inhalational anesthetics, degradation and production of degradation products can occur when sevoflurane is exposed to desiccated absorbents. When a clinician suspects that the CO_2 absorbent may be desiccated, it should be replaced. The color indicator of most CO_2 absorbents may not change upon desiccation. Therefore, the lack of significant color change should not be taken as an assurance of adequate hydration. CO_2 absorbents should be replaced routinely regardless of the state of the color indicator.

As with other halogenated volatile anesthetics, the anesthetic requirement for sevoflurane is decreased when administered in combination with nitrous oxide. Using 50% N_2O, the MAC equivalent dose requirement is reduced approximately 50% in adults, and approximately 25% in pediatric patients.

It is not known whether sevoflurane or its metabolites are present in human milk. To minimize infant exposure to sevoflurane or its metabolites, a nursing mother may temporarily pump, and discard breast milk produced during the first 24 hours after administration of sevoflurane. Exercise caution when administering sevoflurane to a nursing mother.

MAC decreases with increasing age. The average concentration of sevoflurane to achieve MAC in an 80 year old is approximately 50% of that required in a 20 year old.

The concentration of sevoflurane required for maintenance of general anesthesia is age dependent. When used in combination with nitrous oxide, the MAC equivalent dose of sevoflurane should be reduced in pediatric patients.

8.3 Recommendations in existing WHO guidelines

No guidelines by WHO for inhaled anesthetics for surgery.

8.4 Recommendations in other current clinical guidelines

The following is taken directly from the proposed guidelines for long-term volatile anesthetic sedation in critically ill patients supported by ASA/APSF (2021).[13] Their recommendation is that either sevoflurane or isoflurane can be used in the ICU.

Agent Selection: Either Sevoflurane or Isoflurane can be used
Sevoflurane – more expensive, lower blood solubility and thus easier to make rapid adjustments, higher tissue solubility and thus accumulates during long-term administration, more metabolized which can increase fluoride levels during long-term administration.
Isoflurane – less expensive, higher blood solubility, lower tissue solubility, less metabolized.

In addition, in 2022, the ASA had an “Inhaled Anesthetic 2022 Challenge” in which some of the strategies included avoiding the use of the high impact anesthetics desflurane and nitrous oxide.[14]

9.0 REVIEW OF BENEFITS: SUMMARY OF EVIDENCE OF COMPARATIVE EFFECTIVENESS

9.1 Systematic literature search

Numerous searches of the published medical literature databases, including Medline, Embase, Derwent Drug File, Biosis, and SciSearch were conducted utilizing relevant key search terms including ‘sevoflurane’ AND ‘isoflurane’, ‘desflurane’ OR ‘halothane’.

9.2 Summary of available evidence for comparative effectiveness

9.2.1 Ultane (sevoflurane) US Prescribing Information (USPI)

The following information is taken from the US FDA-approved AbbVie label for Ultane (sevoflurane). Please note that labels in other countries may vary from the US label.

Sevoflurane was administered to a total of 3185 patients. The types of patients are summarized as follows in Table 2.

Table 2. Patients Receiving Sevoflurane in Clinical Studies

Type of patient	Number	Studied
Adult	2,223	
Cesarean delivery		29
Cardiovascular and patients at risk of myocardial ischemia		246
Neurosurgical		22
Hepatic impairment		8
Renal impairment		35
Pediatric	962	

Source: Ultane (sevoflurane) US FDA PI.[6]

Adult Anesthesia

The efficacy of sevoflurane in comparison to isoflurane, enflurane, and propofol was investigated in 3 outpatient and 25 inpatient studies involving 3591 adult patients. Sevoflurane was found to be comparable to isoflurane, enflurane, and propofol for the maintenance of anesthesia in adult patients. Patients administered sevoflurane showed shorter times (statistically significant) to some recovery events (extubation, response to command, and orientation) than patients who received isoflurane or propofol.

Mask Induction

Sevoflurane has a nonpungent odor and does not cause respiratory irritability. Sevoflurane is suitable for mask induction in adults. In 196 patients, mask induction was smooth and rapid, with complications occurring with the following frequencies: cough, 6%; breath holding, 6%; agitation, 6%; laryngospasm, 5%.

Ambulatory Surgery

Sevoflurane was compared to isoflurane and propofol for maintenance of anesthesia supplemented with N_2O in two studies involving 786 adult (18-84 years of age) ASA Class I, II, or III patients. Shorter times to emergence and response to commands (statistically significant) were observed with sevoflurane compared to isoflurane and propofol (Table 3).

Table 3. Recovery Parameters in Two Outpatient Surgery Studies[a]

	Study 1		Study 2	
Type of patient	**Sevoflurane/N_2O**	**Isoflurane/N_2O**	**Sevoflurane/N_2O**	**Propofol/N_2O**
Mean maintenance	0.64 ± 0.03	0.66 ± 0.03	0.8 ± 0.5	7.3 ± 2.3
Anesthesia	MAC·hr.	MAC·hr.	MAC·hr.	mg/kg/hr.
Exposure	(n = 245)	(n = 249)	(n = 166)	(n = 166)
Time to emergence (min)	8.2 ± 0.4 (n = 246)	9.3 ± 0.3 (n = 251)	8.3 ± 0.7 (n = 137)	10.4 ± 0.7 (n = 142)
Time to respond to commands (min)	8.5 ± 0.4 (n = 246)	9.8 ± 0.4 (n = 248)	9.1 ± 0.7 (n = 139)	11.5 ± 0.7 (n = 143)
Time to first analgesia (min)	45.9 ± 4.7 (n = 160)	59.1 ± 6.0 (n = 252)	46.1 ± 5.4 (n = 83)	60.0 ± 4.7 (n = 88)
Time to eligibility for discharge from recovery area (min)	87.6 ± 5.3 (n = 244)	79.1 ± 5.2 (n = 252)	103.1 ± 3.8 (n = 139)	105.1 ± 3.7 (n = 143)

Source: Ultane (sevoflurane) US FDA PI.[6]
[a]Results are least-squares mean ± SEM; n = number of patients with recording of recovery events
Abbreviations: MAC = minimum alveolar concentration; SEM = standard error of the mean

Inpatient Surgery

Sevoflurane was compared to isoflurane and propofol for maintenance of anesthesia supplemented with N_2O in two multicenter studies involving 741 adult ASA Class I, II or III (18-92 years of age) patients. Shorter times to emergence, command response, and first post anesthesia analgesia (statistically significant) were observed with sevoflurane compared to isoflurane and propofol (Table 4).

Table 4. Recovery Parameters in Two Inpatient Surgery Studies

	Study 1		Study 2	
Type of patient	**Sevoflurane/N_2O**	**Isoflurane/N_2O**	**Sevoflurane/N_2O**	**Propofol/N_2O**
Mean maintenance	1.27 MAC·hr.	1.58 MAC·hr.	1.43 MAC·hr.	7.0 mg/kg/hr.
Anesthesia	± 0.05	± 0.06	± 0.94	± 2.9
Exposure	(n = 271)	(n = 282)	(n = 93)	(n = 92)
Time to emergence (min)	11.0 ± 0.6 (n = 270)	16.4 ± 0.6 (n = 281)	8.8 ± 1.2 (n = 92)	13.2 ±1.2 (n = 92)
Time to respond to commands (min)	12.8 ± 0.7 (n = 270)	18.4 ± 0.7 (n = 281)	11.0 ± 1.20 (n = 92)	14.4 ± 1.21 (n = 91)
Time to first analgesia (min)	46.1 ± 3.0 (n = 233)	55.4 ± 3.2 (n = 242)	37.8 ± 3.3 (n = 82)	49.2 ± 3.3 (n = 79)
Time to eligibility for discharge from recovery area (min)	139.2 ± 15.6 (n = 268)	165.9 ± 16.3 (n = 282)	148.4 ± 8.9 (n = 92)	141.4 ± 8.9 (n = 92)

Source: Ultane (sevoflurane) US FDA PI.[6]
[a]Results are least-squares mean ± SEM; n = number of patients with recording of recovery events
Abbreviations: MAC = minimum alveolar concentration; SEM = standard error of the mean

Pediatric Anesthesia

The concentration of sevoflurane required for maintenance of general anesthesia is age dependent (see **DOSAGE AND ADMINISTRATION in Ultane [sevoflurane] USPI**). Sevoflurane or halothane was used to anesthetize 1620 pediatric patients aged 1 day to 18 years, and ASA physical status I or II (948 sevoflurane, 672 halothane). In one study involving 90 infants and children, there were no clinically significant decreases in heart rate compared to awake values at 1 MAC. Systolic blood pressure decreased 15%-20% in comparison to awake values following administration of 1 MAC sevoflurane; however, clinically significant hypotension requiring immediate intervention did not occur. Overall incidences of bradycardia [more than 20 beats/min lower than normal (80 beats/min)] in comparative studies was 3% for sevoflurane and 7% for halothane. Patients who received sevoflurane had slightly faster emergence times (12 vs. 19 minutes), and a higher incidence of post-anesthesia agitation (14% vs. 10%). Sevoflurane (n = 91) was compared to halothane (n = 89) in a single-center study for elective repair or palliation of congenital heart disease. The patients ranged in age from 9 days to 11.8 years with an ASA physical status of II, III, and IV (18%, 68%, and 13% respectively). No significant differences were demonstrated between treatment groups with respect to the primary outcome measures: cardiovascular decompensation and severe arterial desaturation. Adverse event data was limited to the study outcome variables collected during surgery and before institution of cardiopulmonary bypass.

Mask Induction

Sevoflurane has a nonpungent odor and is suitable for mask induction in pediatric patients. In controlled pediatric studies in which mask induction was performed, the incidence of induction events is shown in Table 5.

Table 5. Incidence of Pediatric Induction Events

Induction Events (%)	Sevoflurane (n = 836)[a]	Halothane (n = 660)[a]
Agitation	14%	11%
Cough	6%	10%
Breath holding	5%	6%
Secretions	3%	3%
Laryngospasm	2%	2%
Bronchospasm	< 1%	0%

Source: Ultane (sevoflurane) US FDA PI.[6]
[a]Note: n = number of patients

Ambulatory Surgery

Sevoflurane (n = 518) was compared to halothane (n = 382) for the maintenance of anesthesia in pediatric outpatients. All patients received N_2O and many received fentanyl, midazolam, bupivacaine, or lidocaine. The time to eligibility for discharge from post-anesthesia care units was similar between agents.

Cardiovascular Surgery

Coronary Artery Bypass Graft (CABG) Surgery

Sevoflurane was compared to isoflurane as an adjunct with opioids in a multicenter study of 273 patients undergoing CABG surgery. Anesthesia was induced with midazolam (0.1-0.3 mg/kg); vecuronium (0.1-0.2 mg/kg), and fentanyl (5-15 mcg/kg). Both isoflurane and sevoflurane were administered at loss of consciousness in doses of 1.0 MAC and titrated until the beginning of cardiopulmonary bypass to a maximum of 2.0 MAC. The total dose of fentanyl did not exceed 25 mcg/kg. The average MAC dose was 0.49 for sevoflurane and 0.53 for isoflurane.

There were no significant differences in hemodynamics, cardioactive drug use, or ischemia incidence between the two groups. Outcome was also equivalent. In this small multicenter study, sevoflurane appears to be as effective and as safe as isoflurane for supplementation of opioid anesthesia for coronary bypass grafting.

Non-Cardiac Surgery Patients at Risk for Myocardial Ischemia

Sevoflurane-N_2O was compared to isoflurane-N_2O for maintenance of anesthesia in a multicenter study in 214 patients, age 40 to 87 years who were at mild-to-moderate risk for myocardial ischemia and were undergoing elective non-cardiac surgery. Forty-six percent (46%)

of the operations were cardiovascular, with the remainder evenly divided between gastrointestinal and musculoskeletal and small numbers of other surgical procedures. The average duration of surgery was less than 2 hours. Anesthesia induction usually was performed with thiopental (2-5 mg/kg) and fentanyl (1-5 mcg/kg). Vecuronium (0.1-0.2 mg/kg) was also administered to facilitate intubation, muscle relaxation or immobility during surgery. The average MAC dose was 0.49 for both anesthetics. There was no significant difference between the anesthetic regimens for intraoperative hemodynamics, cardioactive drug use, or ischemic incidents, although only 83 patients in the sevoflurane group and 85 patients in the isoflurane group were successfully monitored for ischemia. The outcome was also equivalent in terms of adverse events, death, and postoperative myocardial infarction. Within the limits of this small multicenter study in patients at mild-to-moderate risk for myocardial ischemia, sevoflurane was a satisfactory equivalent to isoflurane in providing supplemental inhalation anesthesia to intravenous drugs.

Cesarean Section

Sevoflurane (n = 29) was compared to isoflurane (n = 27) in ASA Class I or II patients for the maintenance of anesthesia during cesarean section. Newborn evaluations and recovery events were recorded. With both anesthetics, Apgar scores averaged 8 and 9 at 1 and 5 minutes, respectively. Use of sevoflurane as part of general anesthesia for elective cesarean section produced no untoward effects in mother or neonate. Sevoflurane and isoflurane demonstrated equivalent recovery characteristics. There was no difference between sevoflurane and isoflurane about the effect on the newborn, as assessed by Apgar Score and Neurological and Adaptive Capacity Score (average = 29.5). The safety of sevoflurane in labor and vaginal delivery has not been evaluated.

Neurosurgery

Three studies compared sevoflurane to isoflurane for maintenance of anesthesia during neurosurgical procedures. In a study of 20 patients, there was no difference between sevoflurane and isoflurane with regard to recovery from anesthesia. In 2 studies, a total of 22 patients with intracranial pressure (ICP) monitors received either sevoflurane or isoflurane. There was no difference between sevoflurane and isoflurane with regard to ICP response to inhalation of 0.5, 1.0, and 1.5 MAC inspired concentrations of volatile agent during N_2O-O_2-fentanyl anesthesia. During progressive hyperventilation from $PaCO_2$ = 40 to $PaCO_2$ = 30, ICP response to hypocarbia was preserved with sevoflurane at both 0.5 and 1.0 MAC concentrations. In patients at risk for elevations of ICP, sevoflurane should be administered cautiously in conjunction with ICP-reducing maneuvers such as hyperventilation.

Hepatic Impairment

A multicenter study (2 sites) compared the safety of sevoflurane and isoflurane in 16 patients with mild-to-moderate hepatic impairment utilizing the lidocaine MEGX assay for assessment of hepatocellular function. All patients received intravenous propofol (1-3 mg/kg) or thiopental (2-7 mg/kg) for induction and succinylcholine, vecuronium, or atracurium for intubation. Sevoflurane or isoflurane was administered in either 100% O_2 or up to 70% N_2O/O_2. Neither drug adversely

affected hepatic function. No serum inorganic fluoride level exceeded 45 μM/L, but sevoflurane patients had prolonged terminal disposition of fluoride, as evidenced by longer inorganic fluoride half-life than patients with normal hepatic function (23 hours vs. 10-48 hours).

Renal Impairment

Sevoflurane was evaluated in renally impaired patients with baseline serum creatinine > 1.5 mg/dL. Fourteen patients who received sevoflurane were compared with 12 patients who received isoflurane. In another study, 21 patients who received sevoflurane were compared with 20 patients who received enflurane. Creatinine levels increased in 7% of patients who received sevoflurane, 8% of patients who received isoflurane, and 10% of patients who received enflurane. Because of the small number of patients with renal insufficiency (baseline serum creatinine greater than 1.5 mg/dL) studied, the safety of sevoflurane administration in this group has not yet been fully established. Therefore, sevoflurane should be used with caution in patients with renal insufficiency.

9.2.2 Meta-analyses

These studies will primarily present results for sevoflurane compared to inhaled anesthetics on the WHO EML including isoflurane, halothane, and nitrous oxide.

9.2.2.1 Average and Variability of Time to Extubation

Sevoflurane and desflurane were compared to isoflurane in operating room recovery time.[15] A total of 56 previously published articles that included both children and adults were included in the analyses. Results showed that sevoflurane reduced the mean extubation time by 13% and the standard deviation by 8.7% relative to isoflurane. These reductions in the mean and standard deviation would reduce the incidence of prolonged extubation times by 51% and 35%, respectively. Sevoflurane also demonstrated mean and standard deviation reductions in time to following commands by 27% and 26%, respectively, relative to isoflurane. The authors believe the large time difference in following commands could be due to the more soluble isoflurane having a larger residual effect on higher cognitive function. But they also mentioned that there were multiple outliers with sevoflurane that may have contributed to these large differences.

9.2.2.2 Recovery Times from Anesthesia

Nine studies in adults compared sevoflurane (N = 813) to isoflurane (N = 749), which included recovery times, were included in the meta-analyses.[16] Sevoflurane showed statistically significantly shorter times (in minutes) versus isoflurane (mean ± pooled variance [95% CI]) for time of emergence (-2.9 ± 0.1 [-3.1 to -2.7]), endotracheal extubation (-1.6 ± 0.1 [-1.9 to -1.3]), response to commands (-3.0 ± 0.2 [-3.3 to -2.7]), orientation (-4.5 ± 0.2 [-4.8 to -4.2]), and first post-operative analgesic (-8.9 ± 1.0 [-10.8 to -7.0]). Discharge from recovery room did not significantly differ between the 2 anesthetics. A second study included a comparison of sevoflurane versus isoflurane in patients recovery profile after undergoing ambulatory surgery.[17] The meta-analysis included 6 studies (N = 634 patients). Sevoflurane showed statistically significantly (weighted mean difference [95% CI]) shorter times (in minutes) in “time to opening

eyes" (2.4 [1.8 to 2.9], *P*<0.01), "time to obeying commands" (2.4, [1.8 to 2.9], *P*<0.01), "time to transfer from Phase I to Phase II recovery" (8.2 [5.7 to 10.6], *P*<0.01), "home readiness" 5.1 [2.8 to 7.4], *P*<0.00001), and "home discharge" (25 [0.4 to 50], *P*<0.05) compared with isoflurane. In addition, sevoflurane patients showed significantly less post-operative drowsiness than isoflurane. No recovery profile endpoint or post-operative complication was significantly in favor of isoflurane.

9.2.2.3 Cardiac Troponin Levels in Patients Undergoing Cardiac Surgery

Five randomized clinical trials were included in this meta-analysis comparing sevoflurane (N = 190) to isoflurane (N = 191) on their effect on troponin levels in patients (children and adults) undergoing cardiac surgery.[18] Troponin levels are detectable when myocardial damage, such as from a heart attack, has occurred. At admission to the ICU after surgery (baseline was before surgery), troponin levels were 3.63 ng/mL higher for sevoflurane compared to isoflurane (*P*<0.001). Sevoflurane had nonsignificant higher levels of troponin at 6 and 12 hours after ICU admission. Troponin levels were 1.19 ng/mL and 0.36 ng/mL higher with isoflurane at 24 hours (*P*<0.001) and 48 hours (not significant) after ICU admission compared to sevoflurane. When using baseline as arrival in ICU, troponin levels were 0.23 ng/mL and 0.67 ng/mL higher with isoflurane at 24 and 48 hours compared to sevoflurane (both not significant). The authors conclude that the small mean differences between the two anesthetics do not have a negative effect on cardiac troponin levels.

9.2.2.4 Survival after Cardiac Surgery

Studies that compared total intravenous anesthesia (TIVA) to volatile inhaled anesthetics sevoflurane, desflurane and isoflurane for survival after cardiac surgery were included in this Bayesian network meta-analysis.[19] A total of 38 studies in adults were included in the analyses with 1,648 receiving TIVA, 1,025 receiving sevoflurane, 622 receiving isoflurane, and 701 receiving desflurane. Sevoflurane (OR = 0.31, 95% credible interval 0.14-0.64) was associated with a reduced mortality compared to TIVA. Desflurane, but not isoflurane, was also associated with reduced mortality compared to TIVA.

9.2.2.5 Postoperative Outcomes of Cardiac Surgery

Sixteen trials (N = 961 adult patients) were included to evaluate the impact of sevoflurane versus isoflurane on clinically relevant outcomes in patients undergoing cardiac surgery.[20] The length of time in ICU, hospital length of stay, and time to extubation were all non-statistically significantly different between the 2 anesthetics. Levels of S100β and troponin after surgery and 24 hours after surgery were also not significantly different; however, levels of CK-MB 24 hours after surgery was significantly increased (*P*<0.008) with isoflurane than with sevoflurane (SMD of 2.16; 95% CI 0.57 to 3.74). The authors conclude that choosing one anesthetic over the other does not have a significant impact on postoperative outcomes after cardiac surgery.

9.2.2.6 Mortality and Complications after Cardiac and Noncardiac Surgery

A total of 68 publications (N = 7,104 adult patients) were included to determine the effects of volatile anesthetics on mortality and postoperative pulmonary and other complications after cardiac and noncardiac surgery.[21] Overall, volatile anesthetics were associated (all statistically significant) with reduced mortality, less pulmonary complications and less other complications in cardiac surgery compared to TIVA. In noncardiac surgery the volatile anesthetics were not associated with reduced mortality or complications. Sevoflurane was also compared against isoflurane. In cardiac surgery, sevoflurane showed reduced mortality, less pulmonary complications and less other complications compared to isoflurane although none reached statistical significance. In noncardiac surgery, sevoflurane demonstrated reduced mortality and less other complications versus isoflurane but the latter showed less pulmonary complications than sevoflurane; all comparisons were not statistically significant.

9.2.2.7 Effect on Renal Function

Six studies (N = 873 adult patients) were included which compared sevoflurane to isoflurane on kidney function in healthy patients 24 and 72 hours post-anesthesia.[22] There were no statistically significant differences between the groups at either time interval for serum/plasma creatinine, BUN, urinary protein, and glucose excretion. The authors state that sevoflurane has minimal acute nephrotoxic potential. A 2020 meta-analysis used 41 studies that compared sevoflurane to other anesthetics (inhaled and TIVA) that reported results related to renal function.[23] There was no difference found between the groups for creatinine or creatinine clearance at 24 hours. There was also no difference between the groups in BUN at 24 hours. Similar results were found within the subgroups that were analyzed. The authors concluded that sevoflurane use did not increase renal dysfunction compared with other agents used for anesthesia maintenance.

9.2.8 Emergence Agitation in Children

This meta-analysis included children under 12 years of age taking either sevoflurane (N = 1,252) or halothane (N = 1,111) in 23 comparative studies that reported ambulatory procedures.[24] Emergence agitation was significantly more common with sevoflurane in the pooled meta-analysis (OR, 2.21; 95% CI, 1.77 to 2.77; *P*<0.0001). Similar results were found when only including high quality studies (n = 14); pooled OR of 1.82 (95% CI 1.37 to 2.41; *P*<0.0001).

9.2.3 Additional Studies

9.2.3.1 Length of Stay in Hospital

A propensity-matched retrospective study, which included adult patients undergoing non-cardiac surgery from the Cleveland Clinic database, compared length of stay in the hospital for those given sevoflurane versus those given isoflurane.[25] There were 2,898 patients in each treatment group. Hospital length stay (adjusted geometric mean [95% CI]) was significantly longer for isoflurane (2.85 days [2.78-2.93]) compared to sevoflurane (2.55 days [2.48-2.62]; *P*<0.0001).

There was no difference between isoflurane and sevoflurane on the secondary outcome of patient-mean 72-hour verbal response scale pain scores (both groups had a mean score of 3.71 on the 0-10 scale).

9.2.3.2 Global Warming Potential of Inhaled Anesthetics

The objective of the study was to determine the impact of sevoflurane, desflurane and isoflurane on climate change.[2] Various techniques were used to better estimate the global warming potential (GWP) for each gas. The 20-year GWP values (higher number has greater impact) for sevoflurane, isoflurane, and desflurane were 440, 1800, and 6810, respectively. The gases atmospheric lifetime (in years) were estimated to be 1.1, 3.2, and 14.0 for sevoflurane, isoflurane, desflurane, respectively.

9.2.3.3 Effects on Airway Reactivity and Hemodynamics

Patients (N = 64) were anesthetized with either sevoflurane or desflurane at 1.0 and 1.8 MAC to assess changes in airway reactivity (coughing) and in hemodynamics in response to the stimulus of endotracheal tube cuff inflation and deflation.[26] At 1.0 MAC, sevoflurane prevented a moderate or severe response to cuff inflation in 92% of patients compared to 75% of desflurane patients ($P<0.05$). One sevoflurane subject (1.8 MAC) had a mild coughing response to cuff inflation and deflation whereas none had a response with desflurane (1.8 MAC). At 1.0 MAC, heart rate significantly increased in 1/31 sevoflurane patients and 11/30 desflurane patients ($P<0.01$). Mean arterial pressure significantly increased ($P=0.05$) in 1 and 6 patients given sevoflurane and desflurane, respectively. Another study compared 130 patients given either sevoflurane 1-3% or desflurane 3-8% in an air/oxygen mixture to assess recovery times and perioperative coughing.[27] The incidence of perioperative coughing was significantly higher ($P<0.05$) for desflurane (32%) compared to sevoflurane (15%). Post-operative sore throats, surgical-related pain, nausea, and emesis were not significantly different between sevoflurane and desflurane. Recovery times measures were mostly not significantly different between the treatment groups. A third study assessed hemodynamic measures over a 12 minute period in patents taking sevoflurane (2.2% for 2 minutes then 3.3% for 10 minutes) or desflurane (7.2% for 2 minutes and 10.8% for 10 minutes).[28] Mean arterial pressure, heart rate, and cerebral artery blood flow velocity were all significantly greater ($P<0.01$) for desflurane compared with sevoflurane. In addition, other studies have shown that sevoflurane does not impair cerebral auto-regulation up to concentrations of 1.5 MAC,[29] whereas desflurane impairs cerebral auto-regulation at concentrations greater than 0.5 MAC.[30] Another study included 3 groups (N = 27 each group) of patients inhaling 2 MAC of sevoflurane, desflurane, or isoflurane to assess pungency and tolerability.[31] The number of patients coughing (or objected to inhaling the gas) were 1, 20, and 11 for sevoflurane, desflurane, and isoflurane, respectively. When questioned if the gas caused burning, irritation or other discomfort, none of the sevoflurane patients complained whereas 21 and 12 patients died in the desflurane and isoflurane groups. The number of patients completing the study were 27, 7, and 20 for sevoflurane, desflurane, and isoflurane, respectively.

9.2.3.4 Arrhythmias

A study of 45 patients compared 1.0 MAC of sevoflurane to desflurane for arrhythmias after off-pump coronary artery bypass grafting (OPCABG).[32] Supraventricular tachycardia occurred significantly more (P<0.05) in desflurane patients (5/20) compared to sevoflurane patients (0/20). Atrial fibrillation rates were also significantly greater (P<0.05) with desflurane (5/20) compared with sevoflurane (1/20). Other measures including atrial flutter, ventricular tachycardia, ventricular fibrillation, and bradycardia were not significantly different between the patient groups.

9.2.3.5 Time to Induction in Pediatric Patients

A study compared the induction characteristics of maximum initial inspired concentrations of 8% sevoflurane (N = 25) and 5% halothane (N = 26) in children aged 3 months to 3 years.[33] The time (mean seconds, range [SD]) in loss of consciousness was shorter with sevoflurane (72, 40-104 [18]) compared with halothane (76, 50-112 [17]) but did not reach significance (P=0.43). Mean time to acceptance of the face mask and mean time taken to reach complete induction were shorter with sevoflurane but neither reached statistical significance. The number of patients classified of having severe struggling were 10 and 17 in the sevoflurane and halothane cohorts, respectively. Another study compared 2% sevoflurane (N = 31) to 0.75% halothane (N = 32) for induction, maintenance, and recovery in children aged 5-12 years undergoing outpatient dental extractions.[34] These gases supplemented 66% nitrous oxide in oxygen. The time (mean seconds [SD]) to loss of eyelash reflex was significantly shorter with sevoflurane (89 [26]) than halothane (127 [32], P<0.05). Time to eye opening (mean seconds [SD]) after anaethesia was longer with sevoflurane (167 [98]) than halothane (102 [70], P<0.05) but time to walking and standing and discharge time were not significantly different between the 2 cohorts. Complications did not significantly differ between the treatment groups during recovery but nausea was significantly lower in sevoflurane patients (n = 3) than halothane patients (n = 10, P<0.05) after discharge from the hospital. A third study compared sevoflurane (N = 50) and halothane (N = 50) during induction, surgery, and recovery in patients aged 2 to 12 years of age.[35] The time (mean minutes [SD]) to loss of eyelash reflex was significantly shorter with sevoflurane (1.5 [0.6]) than halothane (1.9 [0.5], P=0.0003). The time (mean minutes [SD]) to insertion of mouth prop was significantly longer with sevoflurane (3.9 [1.3]) than halothane (3.5 [0.7], P=0.04). Time to eye opening and time to discharge were slightly shorter for sevoflurane than halothane but both were not statistically different between the cohorts. The incidence of arrhythmias throughout the entire process were significantly greater for halothane (62%) compared with sevoflurane (28%, P<0.0005).

9.2.3.6 Recovery Times in Pediatric Patients

Children undergoing spinal surgery were given either sevoflurane (N = 40) or isoflurane (N = 40) and compared in recovery times.[36] Sevoflurane patients had significantly shorter (mean minutes [SD]) extubation times compared to isoflurane patients (6.4 [3.3] vs 10.7 [4.6], P<0.001). Sevoflurane cohort also had significantly shorter emergence time (7.8 [3.4] vs 12.8 [5.6], P<0.001) and time to full Aldrete score (13.9 [5.3] vs 20.3 [6.5], P<0.001) compared with the isoflurane cohort. Discharge criteria being met and postoperative events were similar between

the cohorts. A second study compared recovery times in children aged 2-24 months (N = 84) after undergoing cleft lip surgery and receiving either sevoflurane or isoflurane.[37] Sevoflurane patients had significantly shorter (mean seconds [SD]) extubation times compared to isoflurane patients (319.9 [120.36] vs 582.9 [249.77], *P*<0.001). The sevoflurane cohort also had significantly shorter spontaneous respiration time (290.52 [118.57] vs 483.24 [237.79], *P*<0.001), hip flexion (168.93 [83.37] vs 290.36 [209.98], *P*<0.001), and eye opening (266.07 [161.75] vs 483.21 [188.85], *P*<0.001). A third study assessed recovery times in children aged 7-18 years old undergoing craniotomy for supratentorial tumor excision.[38] Patients (20 per group) were given either sevoflurane, isoflurane, or desflurane. Sevoflurane patients had significantly shorter (mean minutes [SE]) extubation times compared to isoflurane patients (14.1 [0.79] vs 21.25 [0.69], *P*<0.001). Sevoflurane cohort also had significantly shorter emergence time (11.7 [0.7] vs 15.53 [0.91], *P*<0.001) and time to reach Aldrete score ≥9 (29.25 [1.24] vs 35.6 [0.99], *P*<0.001) compared with the isoflurane cohort. The desflurane cohort also had significantly short times on all 3 measures versus the isoflurane cohort; there were no significant differences between the sevoflurane and desflurane cohorts.

9.2.3.7 Recovery Times in Elderly Patients

A study of 104 elderly patients compared recovery times after receiving either sevoflurane or isoflurane.[39] Sevoflurane patients had significantly shorter (median minutes [range]) extubation times compared to isoflurane patients (8 [2-35] vs 11 [2-35], *P*<0.01). The sevoflurane cohort also had significantly shorter time to eye opening (8.5 [2-57] vs 12.5 [3-47], *P*<0.05) and time to discharge from the post-anesthesia care unit (21 [5-69] vs 27.5 [9-180], *P*<0.01) compared with the isoflurane cohort.

9.3 Assessment of applicability of the available evidence across diverse populations and settings

Sevoflurane was first approved in Japan in 1990 and is currently approved in at least 113 countries worldwide. However, sevoflurane is also marketed by other companies so it might be approved in additional countries. Sevoflurane is approved for use in pediatric and adult patients, including the elderly, and has been used across a wide range of populations.[40] It is used in both inpatient and outpatient surgeries including cardiovascular and non-cardiovascular surgeries. Sevoflurane has a well-known efficacy and safety profile and appears to be cardioprotective in cardiac surgery and potentially protective for some other organs.[41-43]

10.0 REVIEW OF HARMS AND TOXICITY: SUMMARY OF EVIDENCE OF COMPARATIVE SAFETY

Sevoflurane is currently approved in at least 113 countries worldwide. Table 6 shows the use of sevoflurane worldwide from 1 September 1994 through 31 January 2022.

Table 6. Post-Authorization (Non-Clinical Trial) Exposure by Geographic Region

Region	Estimated Cumulative Patient Treatments[a]
EEME&A	135,036,686
JAPAC	229,308,323
Latin America	122,661,480
Western Europe/Canada	437,314,822
United States	262,973,944
Unknown	10,148
Total[b]	**1,187,305,402**

Source: Periodic Safety Update Report (PSUR), 2022.[1]
[a]Exposure dates: 1 September 1994 to 31 January 2022
[b]The total may not match because of rounding
Abbreviations: EEME&A = Eastern Europe, Middle East, Africa; JAPAC = Japan, Asia-Pacific

Sevoflurane has shown a low order of acute toxicity in the various species tested. Repeated exposure studies have likewise demonstrated the safety of this drug. Sevoflurane exposure was not associated with any specific organ toxicity, developmental toxicity or mutagenicity in laboratory animals and is considered safe under expected human therapeutic usage.

As with all potent inhaled anesthetics, sevoflurane may cause dose-dependent cardio respiratory depression. Most adverse events are mild or moderate in severity and transient in duration. Nausea and vomiting have been observed in the postoperative period, common sequelae of surgery and general anesthesia, which may be due to inhalational anesthetic, other agents administered intra-operatively or post-operatively, and to the patient's response to the surgical procedure.

The most commonly reported adverse reactions were as follows:

- In adult patients: hypotension, nausea and vomiting;
- In elderly patients: bradycardia, hypotension and nausea; and
- In pediatric patients: agitation, cough, vomiting and nausea.

All events, at least possibly related to sevoflurane from clinical trials, are displayed in Table 7 by MedDRA System Organ Class, Preferred Term and frequency. The following frequency groupings are used: very common (≥1/10); common (≥1/100 and <1/10); uncommon (≥1/1,000 and <1/100); rare (≥1/10,000 and <1/1,000); very rare (<1/10,000), including isolated reports. The type, severity, and frequency of adverse events in sevoflurane patients were comparable to adverse events in reference-drug patients.

Table 7. Summary of Most Frequent Adverse Drug Reactions in Sevoflurane Clinical Trials

System Organ Class	Frequency	Adverse Reactions
Psychiatric disorders	Very Common	Agitation
Nervous system disorders	Common	Somnolence Dizziness Headache
Cardiac disorders	Very Common Common Uncommon Unknown	Bradycardia Tachycardia Atrioventricular block complete QT prolongation associated with Torsade
Vascular disorders	Very Common Common	Hypotension Hypertension
Respiratory, thoracic and mediastinal disorders	Very Common Common	Cough Respiratory disorder Laryngospasm
Gastrointestinal disorders	Very Common Common	Nausea Vomiting Salivary hypersecretion
General disorders and administration site conditions	Common	Chills Pyrexia
Investigations	Common	Blood glucose abnormal Liver function test abnormal[a] White blood cell count abnormal Fluoride increased[b]
Injury, poisoning and procedural complications	Common	Hypothermia

Source: Sevoflurane Company Core Data Sheet.[44]
[a]Occasional cases of transient changes in hepatic function tests were reported with sevoflurane and reference agents
[b]Transient increases in serum inorganic fluoride levels may occur during and after sevoflurane anesthesia. Concentrations of inorganic fluoride generally peak within two hours of the end of sevoflurane anesthesia and return within 48 hours to pre-operative levels. In clinical trials, elevated fluoride concentrations were not associated with impairment of renal function.

See Section 9.3 for a summary of comparative safety versus relevant comparators.

Sevoflurane should be administered only by persons trained in the administration of general anesthesia. Facilities for maintenance of a patent airway, artificial ventilation, oxygen enrichment, and circulatory resuscitation must be immediately available. Since level of anesthesia may be altered rapidly, only vaporizers producing predictable concentrations of sevoflurane should be used. The concentration of sevoflurane being delivered from a vaporizer should be known. This may be accomplished by using a vaporizer calibrated specifically for sevoflurane. In the event of overdosage, or what may appear to be overdosage, the following action should be taken: discontinue administration of sevoflurane, maintain a patent airway, initiate assisted or controlled ventilation with oxygen, and maintain adequate cardiovascular function.

There is no specific work exposure limit established for sevoflurane. However, the National Institute for Occupational Safety and Health has recommended an 8-hour time-weighted average limit of 2 ppm for halogenated anesthetic agents in general (0.5 ppm when coupled with exposure to N_2O).

Current important identified risks for sevoflurane include the following:

- Cardiovascular changes, including cardiac arrhythmias/cardiac events in pediatric population
- Hepatic disorders
- Malignant hyperthermia (can be treated with dantrolene)
- Perioperative hyperkalemia
- Convulsions
- Patients with history of Pompe's Disease
- Mitochondrial disorders
- Hypothermia

AbbVie conducts systematic standardized surveillance for reports associated with these Important Identified Risks. Reports of these risks are reviewed as cases are received. Reviews of aggregate reports of these risks are also performed on a quarterly basis. No new safety signals have been detected through surveillance activities of these risks coincident with sevoflurane therapy during the current reporting interval. AbbVie will continue to monitor these risks through standardized surveillance.

Current important potential risks for sevoflurane include the following:

- Impact of Desiccated CO_2 absorbents
- Use in neurosurgery
- Neurotoxicity in pediatric patients

There were 7 signals evaluated and closed:

- Pediatric neurotoxicity
- Bradycardia in pediatric patients with Down syndrome
- Bleeding or coagulopathy, including platelet dysfunction
- Low flow gas rates recommendation differences in prescribing information and assessment of potential renal toxicity with low fresh gas flow rates
- Diabetes insipidus
- Anesthesia-induced rhabdomyolysis
- Malignant hyperthermia (pharmacogenomic information)

11.0 SUMMARY OF AVAILABLE DATA ON COMPARATIVE COST AND COST-EFFECTIVENESS

Anesthetics generally contribute to less than 5% of a hospital pharmacy budget and accounts for about 3 to 4% of the cost of a surgical procedure.[45] Direct costs include the price of the inhaled anesthetic and the costs of administration and delivery. For instance, use of a high flow rate during the procedure increases the amount of inhaled anesthetic used as compared to a low flow rate; there are certain advantages of a high flow rate but it does increase the cost.[46] The direct cost would also include how much of the gas is used during procedures. Other cost contributors would include supplies and equipment associated with the particular gases.

Additionally, the costs of the staff required for preparing the anesthetic for surgery, safe delivery of the gas during surgery, and for post-operative observation of the patient. Indirect costs would include treating adverse events that may occur; these would include drugs, supplies, and staff as well as potential extended hospital stay or hospital admission. Therefore, the cost of anesthesia is driven by the choice of volatile agents and depends on several other factors including patient populations, duration of anesthesia, surgical unit stay, cost of delivery system, etc.

AbbVie is not the sole provider for sevoflurane and we are writing this application for the molecule and not the brand. As such, there are different Marketing Authorization Holders (MAHs), including generic manufacturers, and different contracts based on amounts and other classifications, etc. Therefore, any price (range) included in this document may not reflect the totality of price ranges worldwide.

AbbVie prices its medicines to reflect the value they bring to patients, the health system and to society. In setting prices for a given medicine across different health systems, we aim to establish pricing levels that account for unique, complex, and dynamic local environments.

AbbVie's pricing for sevoflurane is competitive and supports access to treatment for patients. The pricing of AbbVie's sevoflurane is often inclusive of anesthetic vaporizer filling systems and servicing. Given the high costs and complexities associated with anesthesia systems and medicines, we practice an inclusive pricing approach to ensure uninterrupted delivery of anesthesia.

AbbVie is committed to ensuring that appropriate, quality, and affordable anesthesia is available to patients who need it, globally, today and for the future.

AbbVie acknowledges that the cost of anesthesia may be driven by the choice of volatile agents, and depends on among other factors, patient populations, duration of anesthesia, surgical unit stay, etc. We have provided a comprehensive list of articles for your review and consideration to inform your decision.[15,25,45-51]

In addition to AbbVie, there are multiple manufacturers and suppliers of sevoflurane that ensures a sustainable supply of sevoflurane.[53]

Sevoflurane and desflurane were compared to isoflurane in operating room recovery time.[15] A total of 56 previously published articles that included both children and adults were included in the analyses. Results showed that sevoflurane reduced the mean extubation time by 13% and the standard deviation by 8.7% relative to isoflurane. These reductions in the mean and standard deviation would reduce the incidence of prolonged extubation times by 51% and 35%, respectively. Sevoflurane also demonstrated mean and standard deviation reductions in time to following commands by 27% and 26%, respectively, relative to isoflurane. Desflurane also showed reduced times compared to isoflurane. The authors discuss how reducing extubation times should result in reduced costs especially when considering the overall number of cases in operating rooms. They state that pharmaceutical purchase cost and other considerations should be included along with the extubation time reductions.

A propensity-matched retrospective study, which included adult patients undergoing non-cardiac surgery from the Cleveland Clinic database, compared length of stay in the hospital for those given sevoflurane versus those given isoflurane.[25] There were 2,898 patients in each treatment

group. Hospital length stay (adjusted geometric mean [95% CI]) was significantly shorter for sevoflurane (2.55 days [2.48-2.62]) compared to isoflurane (2.85 days [2.78-2.93]; *P*<0.0001). In 2013, an additional day in the hospital before discharge would exceed $1,900. The authors discuss the overall cost depends on a number of other variables including acquisition cost of the anesthetic which they state is roughly about $20 more for sevoflurane than isoflurane. However, they point out that cost is minimal compared to other surgical costs. For instance, they mention that (in 2013) the cost of one additional minute of delayed emergence costs about $10 per minute in an operating room. Several meta-analyses have shown that emergence times are significantly shorter with sevoflurane versus isoflurane including in children and the elderly.[15-17, 36-39]

A study published in 1997 did a pharmacoeconomic analysis comparing sevoflurane (N = 25) to isoflurane (N = 22) in patients undergoing elective ambulatory surgery.[53] Nine different charges were included but only 3 showed statistical significance between the two anesthetics. Total mean (SE) charges (US dollars) were not significantly different between sevoflurane ($2,641 [174]) and isoflurane ($2,230 [198]). In 2022, the total charges would likely be significantly higher due to price increases related to the entire surgical process. That could also potentially cause statistically significant differences between sevoflurane and isoflurane on some individual costs as well as overall cost.

A study at a general hospital in England had a goal of reducing greenhouse gases in its operating rooms.[54] They collected data from September 2020 through February 2021. The staff placed posters around the anesthetic rooms showing how to reduce emissions and in December 2020, desflurane was removed as a default vaporizer. Desflurane use dropped from 47% in September 2020 to 20% in February 2021 whereas sevoflurane use increased. There was also a corresponding drop in CO_2 emissions from 57 to 17 kg per theatre case which is equivalent to a monthly reduction of 34,840 kg of CO_2 (based on monthly average of 871 cases). In addition, these changes lead to a monthly savings of more than 1,200 British pounds.

12.0 REGULATORY STATUS, MARKET AVAILABILITY AND PHARMACOPOIEAL STANDARDS

Sevoflurane is a nonflammable liquid anesthetic agent administered by vaporization; indicated for induction and maintenance of general anesthesia in adult and pediatric patients for inpatient and outpatient surgery.

Sevoflurane is currently approved in at least 113 countries worldwide. Please be aware that the following list (see Table 8) only represents countries where AbbVie and/or Maruishi is/are the marketing authorization holder(s), and therefore, the list of countries where sevoflurane is available, might be larger.

Table 8. Worldwide Marketing Authorization Status for Sevoflurane[a]

Market / Country	Authorization Status Date
Albania	1/5/2005
Algeria	12/31/2005
Argentina	6/5/2020

Armenia	2/8/2019
Australia	12/12/1995
Austria	7/25/1996
Azerbaijan	4/8/2008
Bahrain	12/18/1996
Bangladesh	11/9/2016
Belarus	12/31/2008
Belgium	4/8/2011
Bolivia	9/24/2008
Bosnia and Herzegovina	5/17/2013
Botswana	9/9/2008
Brunei Darussalam	10/9/2014
Bulgaria	6/18/2001
Canada	9/18/1995
Chile	7/27/2017
China	12/22/1992
Colombia	8/12/1994
Costa Rica	2/27/1995
Croatia	7/27/1998
Cyprus	11/6/2009
Czech Republic	5/14/1997
Denmark	3/15/1996
Dominican Republic	6/9/2009
Ecuador	5/15/2018
Egypt	7/29/2020
El Salvador	11/7/2017
Estonia	2/25/2000
Ethiopia	4/2/2014
Finland	6/12/1995
France	7/10/1995
Georgia	3/19/2019
Germany	9/20/1995
Ghana	10/4/2018
Greece	1/9/1996
Guatemala	9/26/1994
Gulf Cooperation Council	12/1/2020
Honduras	11/17/2017
Hong Kong	3/1/1996
Hungary	1/1/1998
Iceland	8/26/1996
India	4/11/2018
Indonesia	3/6/1997
Iran	5/14/2005
Iraq	12/15/2013
Ireland	4/19/1995
Israel	8/1/1997
Italy	11/23/1996
Jamaica	12/16/1996

Jordan	11/11/1998
Kazakhstan	8/13/2019
Kenya	10/23/2015
Kosovo	12/16/2015
Kuwait	5/1/1996
Latvia	10/19/2005
Lebanon	3/19/1998
Lithuania	3/5/1999
Luxembourg	9/25/1996
Macao	3/1/1996
Madagascar	2/5/2018
Malaysia	2/27/1997
Malta	5/31/2006
Mauritius	3/28/2001
Mexico	7/14/1994
Montenegro	8/15/2014
Morocco	4/9/2003
Namibia	8/18/2004
Nepal	4/25/2011
Netherlands	8/24/2007
New Zealand	3/7/1996
Nicaragua	11/11/1996
Nigeria	4/10/2019
North Macedonia	9/17/2009
Norway	8/13/1996
Oman	12/29/1998
Panama	2/27/2009
Paraguay	2/13/2009
Peru	8/24/2000
Philippines	12/18/1996
Poland	5/18/2007
Portugal	5/30/1997
Puerto Rico	1/18/2007
Qatar	5/1/1996
Russian Federation	11/25/2004
Saudi Arabia	12/19/2005
Serbia	4/20/2002
Singapore	9/3/2008
Slovakia	6/5/1997
Slovenia	6/2/2000
South Africa	3/27/1996
Spain	4/7/1997
Sri Lanka	11/1/2006
Sweden	9/15/1995
Switzerland	10/17/1995
Taiwan	8/8/2016
Tanzania	9/11/2017
Thailand	1/11/2017

Trinidad and Tobago	12/3/2014
Tunisia	6/5/2013
Turkey	9/19/1996
Uganda	6/10/2011
Ukraine	1/23/2006
United Arab Emirates	12/16/1996
United Kingdom	9/1/1995
United States	6/7/1995
Uruguay	4/4/1995
Uzbekistan	4/5/2011
Venezuela	4/23/1996
Viet Nam	9/19/2017
Zambia	10/22/2010
Zimbabwe	8/23/1999

[a]These are marketing authorizations for AbbVie. Other manufacturers of sevoflurane may have approval in additional countries.

Pharmacopoeial Standards

Sevoflurane is listed in the following pharmacopoeia:

The United States Pharmacopoeia : Catalog No: 1612540 https://store.usp.org/product/1612540

The European Pharmacopoeia: Catalog code Y0001046

The Japanese Pharmacopoeia: 17th Edition page 1550

Sevoflurane is not listed in the following pharmacopoeia:

The British Pharmacopoeia

The International Pharmacopoeia

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Appendices

Letters of Support

Sevoflurane as an essential drug WHO

2022-12-06 WHo Letter for Sevoflurane

Letter of Support Sevoflurane WHO EM

WHO Khaled Yassen Sevoflurane.pdf

Ultane (sevoflurane) USPI

Ultane pi August 2022.pdf

Periodic Safety Update Report (PSUR) for sevoflurane

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