

A.41	Sevoflurane – general anaesthesia – EML and EMLc
Draft recommendation	<p><input checked="" type="checkbox"/> Recommended</p> <p><input type="checkbox"/> Not recommended</p> <p>Justification:</p> <p>This Application refers to the inclusion of sevoflurane in the WHO Model List of Essential Medicines (EML) as inhalational gas under anesthetics, preoperative medicines, and medical gases in adult and pediatric patients. Two inhaled anesthetics, halothane and isoflurane, are included in the EML at the moment. Halotane is no longer used in many countries due to its side effect profile.</p> <p>Sevoflurane is indicated for induction and maintenance of general anesthesia in adult and pediatric patients for inpatient and outpatient surgery. The precise mechanism of action of sevoflurane has not been fully elucidated. Like other halogenated inhalational anesthetics, sevoflurane induces anesthesia by binding to ligand-gated ion channels and blocking central nervous system neurotransmission. It has been suggested that inhaled anesthetics enhance inhibitory postsynaptic channel activity by binding GABAA and glycine receptors, and inhibit excitatory synaptic channel activity by binding nicotinic acetylcholine, serotonin, and glutamate receptors (https://go.drugbank.com/drugs/DB01236).</p> <p>This is not the first application for the inclusion of sevoflurane on the WHO EML. Together with other inhalational anesthetics, a previous application (2011) has been proposed, and rejected for sevoflurane (for costs) as well as for enflurane (due to the risks of convulsions).</p> <p>The role of inhaled anesthetics compared to intravenous anaesthesia is often discussed, with some observers stressing that only cultural habits prevent the abandonment of inhaled anesthetics (White et al., Anaesthesia 2020, 75, 451–454. All volatile anaesthetics are potent greenhouse gases, ranging in global warming potential (GWP, a term used to describe the relative potency, molecule for molecule, of a greenhouse gas, taking account of how long it remains active in the atmosphere) from 151 (halothane) to 6440 (desflurane). Sevoflurane has a GWP of 685, isoflurane 1800. As comparison, methane - emitted by livestock around the world and other processes - has a GWP of 84 (https://ozone.unep.org/sites/default/files/2019-05/SAP-2018-Assessment-report.pdf).</p> <p>Clinical efficacy and safety of sevoflurane appears to be like isoflurane, with consistent findings across type of surgery and setting. Prices seem to have decreased in the last decade, but clear indication of its cost effectiveness were not provided.</p> <p>In conclusion, this Reviewer believes sevoflurane is a more costly alternative to other inhaled anesthetics, with a comparable benefit/harm profile and better environmental impact. The Panel may consider including sevoflurane as a squared box alternative of isoflurane. Appropriate means for administration, monitoring and disposal are needed for a cost effective and safe use of sevoflurane.</p>

<p>Does the proposed medicine address a relevant public health need?</p>	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>The use of anesthetic agents in operating rooms and intensive care units is a very common medical practice that carries important risks. Quality and safety in this field have improved, thanks to better delivery equipment, monitoring practice, airway management, training, and the introduction of anesthetic drugs, characterized by shorter and more predictable onset and offset times and fewer side effects.</p> <p>While intravenous and locoregional anesthesia (whenever possible) are the preferred procedures, induction and maintenance using volatile anesthetics may still offer advantages in some situations. For instance, inhalational anesthesia is indicated most often in children and adults in whom it is difficult to obtain intravenous access.</p>
<p>Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication?</p> <p>(this may be evidence included in the application, and/or additional evidence identified during the review process)</p>	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>Adults</p> <p>According to the Application, 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.</p> <p>Compared to isoflurane, results from meta-analysis showed that</p> <ul style="list-style-type: none"> • sevoflurane reduced the time to patients' recovery, measured as time to endotracheal extubation, response to commands orientation, and first post-operative analgesic, but not the time to discharge from the operating room; • in patients undergoing cardiac surgery, there were no difference in cardiac troponin levels, length of time in ICU, hospital length of stay, and time to extubation. • no important differences in mortality, pulmonary complications or other complications. However, overall, volatile anesthetics were associated with reduced mortality, less pulmonary complications and less other complications in cardiac surgery compared to total intravenous anesthesia (TIVA). <p>Children</p> <p>Sevoflurane was compared to halothane and no major differences emerged. Children undergoing spinal surgery treated with sevoflurane had significantly shorter extubation times compared to those with isoflurane.</p> <p>Sevoflurane can be used in asthmatic patients to help relax the airways on induction as they do not have such pungent smells.</p>

<p>Does adequate evidence exist for the safety/harms associated with the proposed medicine?</p> <p>(this may be evidence included in the application, and/or additional evidence identified during the review process)</p>	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>The most common adverse effects of inhaled anesthetic agents are postoperative nausea and vomiting. Intravenous anesthesia instead of inhaled agents reduces the risk of these effects. Other very common adverse events are agitation, bradycardia and hypotension, cough.</p> <p>Other important potential risks for sevoflurane include:</p> <ul style="list-style-type: none"> • Impact of desiccated CO2 absorbents • use in neurosurgery • neurotoxicity in pediatric patients • nephrotoxicity in critically ill patients
<p>Are there any adverse effects of concern, or that may require special monitoring?</p>	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>Cardiovascular changes, including cardiac arrhythmias/cardiac events, hepatic disorders, malignant hyperthermia, perioperative hyperkalemia, convulsions.</p> <p>The concentration of sevoflurane required for maintenance of general anesthesia is age dependent.</p>
<p>Are there any special requirements for the safe, effective and appropriate use of the medicines?</p> <p>(e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)</p>	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>As with all inhaled anesthetics, 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.</p> <p>There is the necessity to advocate for a wider availability of means of administration (vaporizers), monitoring (gas analysers) and absorption (scavenging systems).</p>

<p>Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>The Application does not report a clear analysis of the cost effectiveness. Data from International Medical Products Price Guide (last update 2015) reports a decrease in the price of sevoflurane, that however remains approximately twice that of isoflurane.</p> <p>SEVOFLURANE (buyer medians)</p> <p>Median Price: 0.3146/ml ↓ 23%; High/Low Ratio: 1.45; Lowest Price: 0.2563/ml; Highest Price: 0.3729/ml</p> <p>https://mshpriceguide.org/en/single-drug-information/?DMFId=1030&searchYear=2015</p> <p>ISOFLURANE (buyer medians)</p> <p>Median Price: 0.1514/ml ↓ 31%; High/Low Ratio: 10.13; Lowest Price: 0.0673/ml; Highest Price: 0.6816/ml</p> <p>https://mshpriceguide.org/en/single-drug-information/?DMFId=918&searchYear=2015</p> <p>Sevoflurane (and desflurane) are substantially more expensive than isoflurane at fresh gas flow rates ranging from 1 L/min to 3 L/min, calculating the cost per minimum alveolar concentration (MAC) hour, defined as administration of the inhaled anesthetic agent at 1 MAC for one hour.</p>
<p>Are there any issues regarding the registration of the medicine by national regulatory authorities?</p> <p>(e.g. accelerated approval, lack of regulatory approval, off-label indication)</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>Sevoflurane is approved in several countries worldwide (more than 110) and generics are available.</p>
<p>Is the proposed medicine recommended for use in a current WHO guideline?</p> <p>(refer to: https://www.who.int/publications/who-guidelines)</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>No guidelines by WHO for inhaled anesthetics for surgery</p>