### A.41 Sevoflurane – general anaesthesia – EML and EMLc

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<tr>
<th>Draft recommendation</th>
<th>☒ Recommended</th>
<th>☐ Not recommended</th>
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<tbody>
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<td>Justification:</td>
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<td>Global estimates from 2016 suggests that, approximately 6% of the world’s population requires surgery and that anaesthesia will be required for about 92% of the surgeries. Sevoflurane is an effective inhalational gas anaesthetic which is also more environmentally friendly than its peers. Sevoflurane performs well compared to its peers already in the EML (halothane, nitrous oxide, and isoflurane). Sevoflurane is indicated for induction and maintenance of general anaesthesia in adult and paediatric patients for inpatient and outpatient surgery. Over 1 billion people globally have been exposed to sevoflurane. Meta-analysis suggests that sevoflurane reduced the mean extubation time by 13% and time to following commands by 27% compared to peers.</td>
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<tr>
<th>Does the proposed medicine address a relevant public health need?</th>
<th>☒ Yes</th>
<th>☐ No</th>
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<tr>
<td>Comments: Globally, approximately 6% of the world’s population requires surgery and that anesthesia will be required for about 92% of the surgeries. 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 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. 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. 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.</td>
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Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication?

☒ Yes
☐ No
☐ Not applicable

Comments:

**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 N2O 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.

**Inpatient Surgery**

Sevoflurane was compared to isoflurane and propofol for maintenance of anesthesia supplemented with N2O 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.

**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.
Does adequate evidence exist for the safety/harms associated with the proposed medicine?
☐ Yes
☐ No
☐ Not applicable

Comments: 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. 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.

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. 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. 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.

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. 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).

Are there any adverse effects of concern, or that may require special monitoring?
☐ Yes
☒ No
☐ Not applicable

Comments:
### Expert review

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<th>Question</th>
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<td>Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)</td>
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<td>Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?</td>
<td>☐ Yes</td>
<td>☒ No</td>
<td>☐ Not applicable</td>
<td>Comments: Anaesthetics usually cost a small part of surgical services</td>
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<td>Are there any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)</td>
<td>☐ Yes</td>
<td>☒ No</td>
<td>☐ Not applicable</td>
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<td>Is the proposed medicine recommended for use in a current WHO guideline? (refer to: <a href="https://www.who.int/publications/who-guidelines">https://www.who.int/publications/who-guidelines</a>)</td>
<td>☐ Yes</td>
<td>☒ No</td>
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