### Reviewer No.1 checklist, section reviews

#### Section 20: Muscle relaxants (peripherally acting) and cholinesterase inhibitors

<table>
<thead>
<tr>
<th>Proposed 'Green' medicines</th>
<th>Proposed 'yellow' medicines</th>
<th>Proposed 'red' medicines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neostigmine, tablet, 15mg (bromide); injection, 500 micrograms in 1-ml ampoule; 2.5mg (metilsulfate) in 1-ml ampoule</td>
<td></td>
<td>Pyridostigmine, tablet, 60mg (bromide); injection, 1mg in 1-ml ampoule</td>
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<tr>
<td>Suxamethonium, injection, 50mg (chloride)/ml in 2-ml ampoule; powder for injection (chloride), in vial</td>
<td></td>
<td>vecuronium, powder for injection, 10mg (bromide) in vial</td>
</tr>
</tbody>
</table>

**For proposed 'greens': Is there any reason not to endorse these as essential medicines for children?**

- Do these medicines meet a public health need?  
  - Neostigmine: Yes ☒ No ☐  
  - Suxamethonium: Yes ☒ No ☐  
  - Vecuronium: Yes ☒ No ☐

- Are they registered for use in (all age categories of) children?  
  - Neostigmine: Yes ☒ No ☐  
  - Suxamethonium: Yes ☒ No ☐  
  - Vecuronium: Yes ☒ No ☐

- Are there any unanswered/unexpected clinical issues with respect to effectiveness or safety?  
  - Neostigmine: Yes ☒ No ☐  
  - Suxamethonium: Yes ☒ No ☐  
  - Vecuronium: Yes ☒ No ☐

- Are there special requirements or training needed for safe/effective use?  
  - Neostigmine: Yes ☒ No ☐  
  - Suxamethonium: Yes ☒ No ☐  
  - Vecuronium: Yes ☒ No ☐
Additional comments if any:
Neostigmine: (1) 2005 EML expert panel review: The Committee recommended that neostigmine metilsulfate be retained on the Model List, (2) Safety and efficacy of neostigmine metilsulfate injection and neostigmine bromide tablets has not been established in children (Prod Info Prostigmin(R), 2000a) (3). Pyridostigmine is considered by most clinicians to be the drug of choice for oral administration because of its longer duration of action and reportedly lower incidence of adverse muscarinic effects. (4) No oral liquid formulation (UK – Extemporaneous preparation)  
Suxamethonium: (1) 2005 EML expert panel review: The Committee recommended that suxamethonium chloride be retained on the Model List, (2) Martindale: Reports of fatal cardiac arrests (1,2) in apparently healthy children and adolescents, who were subsequently found to have had undiagnosed myopathies, led to restrictions in the USA on the use of suxamethonium in this age group. Suxamethonium was contra-indicated except for emergency tracheal intubation or where an immediate securing of an airway was essential. Many anaesthetists disagreed (2) with this contra-indication and an FDA Committee advised (3) that it should be replaced by a warning about the possibility of cardiac arrest associated with hyperkalaemia with special attention being paid to male children who are considered to be at the highest risk.  
Vecuronium: Pancuronium is the preferred agent in patients WITHOUT a history of renal failure or cardiovascular disease (eg ischemic heart disease or arrhythmias). Vecuronium is an excellent alternative in patients that do not meet the pancuronium guidelines. Vecuronium’s advantages include superior cardiovascular stability and favorable renal pharmacokinetics. Both agents insignificantly affect histamine release and are therefore preferred in patients with hyperactive airway disease. Atracurium is generally reserved for patients with multiple organ dysfunction or with contraindications to vecuronium or pancuronium (Clarens et al, 1993). The cost of these agents is drastically different. For example, atracurium and vecuronium are 3 to 4 times the cost of pancuronium.  

Action proposed for the Committee to take:  
Neostigmine: Endorse neostigmine methylsulfate injection as essential for reversal of non- depolarizing neuromuscular block. Neostigmine bromide – flag for detailed review for comparison of its efficacy and safety in contrast to pyridostigmine in the treatment of myasthenia gravis  
Suxamethonium: Endorse as essential for muscular relaxation during surgery. Recommend detailed review of literature on the risk of hyperkalaemia and fatal cardiac arrests in “apparently” healthy children  
Vecuronium: Need a detailed review comparing vecuronium, pancuronium and atracurium for efficacy, safety, cost and pharmacoeconomics before endorsing one
For “red’ medicines: Are these potentially essential medicines for children?

Do these medicines meet a public health need?

- Pyridostigmine: Yes ☐ No ☐
- Alcuronium: Yes ☐ No ☐—if No further comments needed

If they meet a public health need, what is needed?

- Product development of an appropriate dosage form: Pyridostigmine: Yes ☐ No ☐
  
If, Yes – suggest what might be needed?:
- Pyridostigmine: oral paediatric formulation (see the comments with neostigmine)
- Regulatory approval (ie clinical trial) exist? Pyridostigmine: Yes ☐ No ☐

Clinical trials of efficacy and safety in children?
- Pyridostigmine: Yes ☐ No ☐

Additional comments if any: Alcuronium: Choice of non-depolarizing blocker for paediatric use needs detailed review. However, in previous EML panel, the committee noted that no systematic review is available to validate the comparative efficacy and safety of alcuronium and vecuronium. The ISDB reviewer indicated that vecuronium offers advantages over alcuronium (57), and is therefore a better representative of neuromuscular blocking agents than alcuronium. However, the Committee noted that vecuronium is relatively expensive compared with the other alternatives. In view of the above considerations the Expert Committee recommended that alcuronium and vecuronium be retained with a square box on the Model List, and that a footnote should be added to alcuronium stating that alternative medicines for its possible replacement will be reviewed at its next meeting in 2007. BNF- C favors pancuronium and atracurium (see the comments given with vecuronium as well)

Action proposed for the committee to take:
- Pyridostigmine: Flag for detailed review for comparison of its efficacy and safety in contrast to neostigmine in the treatment of myasthenia gravis (? Paediatric formulation)
- Alcuronium: Can be removed from the model list for children