Reviewer 1: Antiemetic Medicines for Children (Section 17.2)

The Proposal for the Inclusion of Anti-emetic Medications (for Children) is a summary of 25 systemic reviews of the treatment of postoperative nausea and vomiting in children. There were no proposals for inclusion on the Model List of any specific drugs or dosage forms in this paper.

If one reviews the data on efficacy, then ondansetron with dexamethasone is the most effective regimen with an odds ratio having nausea of vomiting of around 0.2 when compared to placebo. Dexamethasone alone had a relative risk of 0.5 compared to placebo and ondansetron alone was better than metoclopramide with a relative risk of 0.5. A variety of other drugs reviewed had fewer efficacies than these. At this reviewer’s institution, the customary therapy for postoperative nausea and vomiting in children is ondansetron with dexamethasone added if necessary.

The toxicities of all of the drugs considered are well listed in the Proposal paper. One fact noted is that “The safety of most of these treatments has not been adequately established in children less than 2 years of age (the most notable exception is ondansetron which is approved by the FDA for children greater than 1 month of age).” There are specific toxicities in some government documents.

- droperidol and cardiotoxicity (USA)
- dolasetron and cardiotoxicity
- metoclopramide and extrapyradmidal side effects (Australia)

The 15th Model List includes two drugs as anti-emetics in section 17.2, metoclopramide and promethazine. Methoclopramide compared to placebo had relative risks of vomiting of 0.5 and odds ratios for protection of 3.0 - 6.0 at doses of 0.1-0.25 mg/kg. There were no data on efficacy of promethazine in the Proposal. One study comparing promethazine to prochlorperazine in gastroenteritis vomiting found prochlorperazine to be better. A study of 87 healthy adults having middle ear surgery found promethazine reduced the frequency of vomiting from 74% (placebo) to 39% on promethazine and 24% on ondansetron (Khalil, et al. J Clin Anesth 1999; 11: 596-600). Another study, observational in nature, failed to detect benefit from promethazine or dimenhydrinate in suppressing vomiting after tonsillectomy in children (Scarlett M, et al. West Indian Medical J 2005; 54: 59-64).

In the opinion of this reviewer based on the data about metoclopramide in the Proposal and the data described above about promethazine, both drugs have efficacy for the treatment of postoperative nausea and vomiting. Neither is a good as ondansetron or dexamethasone. Young people are more sensitive to the extrapyramidal effects of metoclopramide that older people but these are well known and can be managed with medications if necessary.

Dexamethasone is cheap available parenterally and is listed in two places in the 15th Model List at 4 mg/ml already. It should remain on the List and be added to section 17.2. Ondansetron is the most effective postoperative anti-emetic, especially if given with dexamethasone, of all those regimens reviewed in the Proposal. It is more expensive now than the other classes of antiemetics that were reviewed. The Proposal indicates that it will go off patent in some jurisdictions “soon”. In the recent past, the Expert Committee has not used high price a criterion for rejecting a drug that would otherwise be considered essential. Since this is the most effective single agent for this indication, I recommend that ondansetron, 2 mg/ml be added to section 17.2 of the Model List.

Promethazine with the equivalent of a square box was listed as the only antiemetic in the first Model List in 1977. In the 1970 edition of Goodman and Gilman, antihistamines are listed as being
effective for motion sickness and they “have found some use as antiemetics in the control of postoperative vomiting”. I suspect this was the basis for their inclusion in the original List. The square box was present up to the 2002 List but removed in the 2003 List without explanation. Research has found that receptors for histamine, acetylcholine, and serotonin are involved in vomiting so it is not irrational to consider that antihistamines have some antiemetic effect. The 2006 edition of Goodman and Gilman states that antihistamines (H1 blockers) act on vestibular afferents and in the brainstem (unreferred). This book also states that H1 blockers are effective in motion sickness. Reviews by Wood, et al (Aerospace Med 1965; 36:1-4 and JAMA 1966; 198: 122-6) present lots of clinical trial evidence that H1 blockers and muscarinic blockers are quite effective in treating motion sickness. Motion sickness is due to vestibular nerve impulses. The other pathway for vomiting to occur is through signals from the chemoreceptor trigger zone. Apomorphine is the prototype stimulus for this cause of vomiting and trimethobenzamide and other dopamine D2 receptor blockers have been the standard treatment for this type of vomiting. The serotonin 5-HT3 receptors (ondansetron class) also act on this this pathway of vomiting.

At present, the List contains an H1receptor blocker and a D2 receptor blocker, one for motion sickness and one for CTZ triggered vomiting. Ondansetron appears to be a better CTZ-triggered vomiting blocker that metoclopramide which is why I urge it be added to this part of the Model List. The most effective antihistamines for motion sickness were meclizine and cyclizine (Aerospace med, op cit). If the policy of the Expert Committee is not to change the List unless there is a good reason, then promethazine can remain as an antiemetic. Since cyclizine is a more effective antiemetic and approved in the US for children 6 years old and older, I would suggest we keep antihistamine H1 blockers on the Model List as an antiemetic for motion sickness but replace promethazine with cyclizine. The item is 25 mg tablets. A square box may be added since other in the H1 blockers also work.

The pharmacology of these classes of drugs with the understanding of the physiology of vomiting by two separate pathways can explain why promethazine was effective for vomiting following ear surgery and not effective following tonsillectomy.

If these suggestions are followed, the revised Model List would include in section 17.2:
metoclopramide as already described (5 mg in 2 ml ampule and10 mg tablets)
ondansetron 2 mg/ml in 2 ml ampules and 4 mg tablets for children and adults and 8 mg tablets for adults if desired
dexamethasone 4 mg/ml
cyclizine with square box 25 mg tablet

I suggest a footnote or explanatory note that the cyclizine is for motion sickness and the other three are for postoperative and cancer chemotherapy-induced vomiting.