

**Second Meeting of the Subcommittee of the Expert Committee on the  
Selection and Use of Essential Medicines**

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**PROPOSAL FOR THE INCLUSION OF ANTI-EMETIC MEDICATIONS  
(FOR CHILDREN) IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES**

**REPORT**

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**1. Summary statement of the proposal**

Anti-emetic medications (anti-histamines, dopamine antagonists and serotonin 5-HT<sub>3</sub> antagonists) are proposed for inclusion in the World Health Organization (WHO) Model List of Essential Medicines for the management of acute gastroenteritis in children.

**2. Name of focal point in WHO submitting or supporting the application****3. Name of the organisation preparing the application**

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**4. International Nonpropriety Name (INN, generic name) of the medicine**

The proposal reviews relevant data regarding four anti-emetic medications; metoclopramide and domperidone (dopamine agonists), promethazine (anti-histamine) and ondansetron (serotonin 5-HT<sub>3</sub> antagonist).

**5. Formulation considered for inclusion**

The formulations of metoclopramide, domperidone, promethazine and ondansetron considered for inclusion are shown in Table 1.

**Table 1: Formulations of ant-emetic medications considered for inclusion**

	<b>Formulation</b>	<b>Comment</b>
Metoclopramide	Injection or oral preparation (tablet, oral liquid, drops)	- Injection, tablet and oral liquid formulations are currently listed on WHO EML for children. - Metoclopramide (in any form) is not recommended for use in neonates.
Promethazine	Injection, oral preparation (tablet, oral liquid) or suppository	- Injection, tablet and oral liquid formulations are currently listed on WHO EML for children. - Includes the use of promethazine hydrochloride and promethazine teoclate - Promethazine (in any form) is not recommended for use in children < 2 years of age.
Domperidone	Oral preparation (tablet, oral liquid) or suppository	- No formulation is currently listed on WHO EML for children - Domperidone injections are not recommended for use in children
Ondansetron	Injection or oral preparation (tablet, disintegrating tablet, oral liquid)	- No formulation is currently listed on WHO EML for children

Source: Freedman & Fuchs (2004); MARTINDALE<sup>®</sup> drug evaluations ([www.micromedex.com](http://www.micromedex.com)); WHO Model List of Essential Medicines for Children (October 2007).

**6. International availability**

Generic versions of domperidone maleate, metoclopramide hydrochloride, ondansetron hydrochloride and promethazine are available worldwide. Promethazine is currently available with two different salts; promethazine hydrochloride and promethazine teoclate. The common brand names associated with each drug are presented in Appendix A.

## 7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Three classes of anti-emetic medications used in the management of paediatric acute gastroenteritis are considered for listing on the Model List of Essential Medicines; dopamine agonists (metoclopramide and domperidone), anti-histamines (promethazine) and serotonin 5-HT<sub>3</sub> antagonists (ondansetron). Members of each therapeutic class are listed in Table 2.

**Table 2: Anti-emetic medications**

Drug class	Anti-emetic agent
Dopamine antagonists	Domperidone, droperidol, haloperidol, metoclopramide, prochlorperazine
Anti-histamines	Dimenhydrinate, promethazine
Serotonin 5-HT <sub>3</sub> antagonists	Dolasetron, granisetron, ondansetron, tropisetron

## 8. Information supporting the public health relevance

### 8.1 Disease burden

Gastroenteritis is an acute disease of the gastrointestinal tract typically caused by a viral or bacterial pathogen leading to diarrhoea and/or vomiting.

Gastroenteritis is one of the leading causes of childhood mortality and morbidity worldwide. According to the WHO approximately 3-5 billion diarrhoeal disease cases occur every year in children less than 5 years of age. This results in approximately 1.5 million deaths each year in young children (WHO, 2004). In the United States alone it is estimated that approximately 3 million children suffer from gastroenteritis each year, resulting in 1.5 million outpatient consultations and 200,000 hospital admissions (CDC, 2003).

Malnutrition, co-morbidities and inadequate access to appropriate care are expected to increase the mortality and morbidity associated with gastroenteritis.

### 8.2 Current treatments

Current clinical practice for the management of acute gastroenteritis focuses on maintaining adequate levels of hydration (as diarrhoea and vomiting can lead to dehydration). For patients with mild or moderate dehydration this may involve the use oral replacement therapy (ORT) to restore fluid and electrolyte levels. Oral replacement solutions (ORS) are available commercially and can also be prepared locally using guidance from current clinical guidelines (CDC 2003, ESPGHAN 2008, WHO 2005).

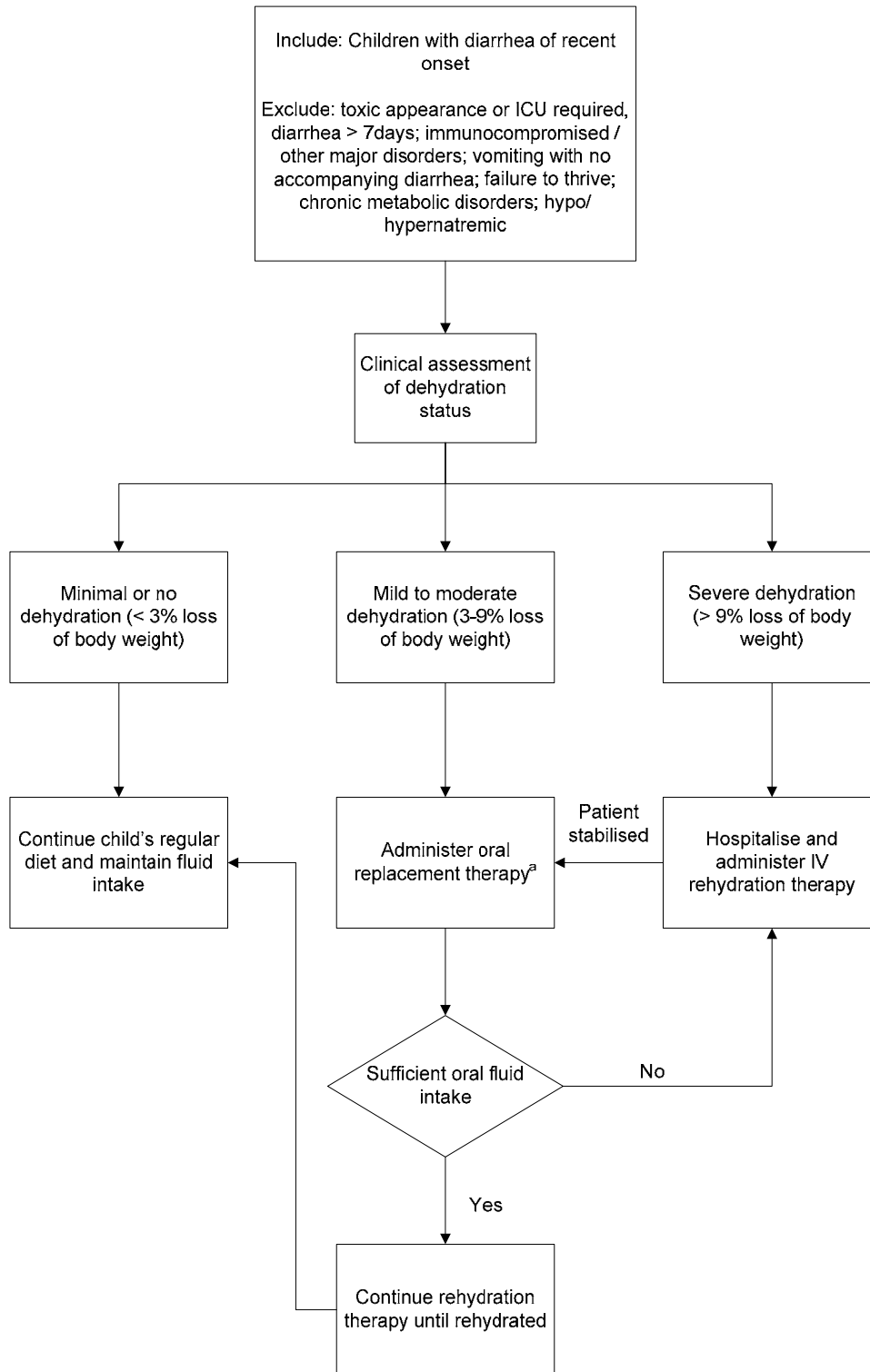
Rehydration therapy may also be administered intravenously (IV) to restore fluid levels quickly in patients failing ORT or experiencing severe dehydration. While IV rehydration is currently regarded as the optimal therapy in these patients it is not without risks and adverse events have been reported relating to cannulation (infiltration at the cannula site infection, pain, bleeding, physical and emotional trauma) and fluid administration (electrolyte disturbances due to inappropriate composition, rate of administration or volume of fluid leading to hyponatraemia, or fluid overload) (Elliot 2007).

Other treatments such as zinc supplementation, probiotics, anti-emetic drugs, anti-diarrhoeal drugs and antibiotics are also used in clinical practice to assist in the management of acute gastroenteritis. The WHO currently recommends the use of zinc supplementation in all children with diarrhoea.

### **8.3 Treatment guidelines**

A simplified treatment algorithm for the management of acute gastroenteritis in children is shown in Figure 1. Anti-emetic medications are not currently recommended for routine use in children with gastroenteritis and are therefore not included in the clinical management algorithm. A number of trials have investigated the use of anti-emetic medications at two different stages of the treatment algorithm:

- In combination with oral replacement therapy (Cubeddu *et al* 1997, Ramsook *et al* 2002, Freedman *et al* 2006, NCT00120744)
- In combination with IV replacement therapy (Reeves *et al* 2002, NCT00691275)



**Figure 1: Clinical pathway for the management of children with acute gastroenteritis**  
 Note: Simplified treatment algorithm modified from the algorithm published by the Cincinnati Children's Hospital Medical Center ([www.cincinnatichildrens.org](http://www.cincinnatichildrens.org)).  
<sup>a</sup> With or without nasogastric tube, as appropriate

Numerous local and regional guidelines for the treatment of acute gastroenteritis in children are available. Table 3 summarises the recommendations of guidelines released by the American Academy of Paediatrics (AAP), US Centres for Disease Control (CDC), European Society for Paediatric Gastroenterology, Hepatology and

Nutrition (ESPGHAN) and the WHO Health Organisation (WHO). None of the guidelines recommend the routine use of anti-emetic medications. However both the CDC and ESPGHAN guidelines indicate that there is some clinical evidence for the effectiveness of ondansetron in the management of acute gastroenteritis. It is unclear whether the WHO guidelines reviewed the evidence related to 5-HT<sub>3</sub> antagonists such as ondansetron.

**Table 3: Clinical guidelines for the management of children with acute gastroenteritis**

Source	Summary
AAP (1996)	<p>The review committee recommended the use of oral rehydration therapy in children experiencing mild to moderate dehydration. The committee also recommended the use of early feeding of appropriate foods. IV rehydration therapy is used for children with severe dehydration or patients unsuccessfully treated with oral rehydration therapy.</p> <p>The review committee recommended against the use of anti-diarrheal agents in children</p> <p>The review committee did not evaluate anti-emetic drugs however the committee did report that “consensus opinion is that anti-emetic drugs are not needed. Physicians who feel that anti-emetic therapy is indicated in a given situation should be aware of potential adverse effects.”</p>
CDC (2003) <sup>a</sup>	<p>The guideline concluded that oral rehydration therapy and early feeding of appropriate foods has been proven effective for the treatment of acute gastroenteritis. IV rehydration therapy is used for children with severe dehydration or patients unsuccessfully treated with oral rehydration therapy.</p> <p>Supplemental zinc therapy and probiotics may have a beneficial effect in the treatment of gastroenteritis</p> <p>Antibiotics, anti-diarrheal agents and anti-emetic drugs are usually unnecessary in the management of acute gastroenteritis. However it was noted that ondansetron (an anti-emetic) can be effective in decreasing vomiting and limiting hospital admission. The authors also suggested that “reliance on pharmacologic agents shifts the therapeutic focus away from appropriate fluid, electrolyte, and nutritional therapy, can result in adverse events, and can add unnecessarily to the economic cost of illness.”</p>
ESPGHAN (2008) <sup>b</sup>	<p>The guideline recommended the use of rehydration therapy (oral or IV, as appropriate) as soon as possible. The guideline also recommended that regular feeding of children should not be interrupted.</p> <p>Selected probiotics may have a beneficial effect in the treatment of gastroenteritis.</p> <p>The guideline concluded that drugs are generally not necessary. The committee stated that “despite some clinical benefits, we suggest that anti-emetics should not be routinely used to treat vomiting during [acute gastroenteritis] in children”</p>

Source	Summary
WHO (2005)	<p>The guideline suggested that zinc supplementation, oral rehydration therapy and early feeding of appropriate foods are effective for the treatment of acute gastroenteritis. IV rehydration therapy is used for children with severe dehydration or patients unsuccessfully treated with oral rehydration therapy.</p> <p>The guideline concluded that “Anti-diarrhoeal drugs and anti-emetics have <i>no practical benefits</i> for children with acute or persistent diarrhoea. They do not prevent dehydration or improve nutritional status, which should be the main objectives of treatment. Some have dangerous, and sometimes fatal, side-effects. These drugs should <i>never</i> be given to children below 5 years.”</p>

Abbreviations: AAP, American Academy of Paediatrics; CDC, Centres for Disease Control; ESPGHAN, European Society for Paediatric Gastroenterology, Hepatology and Nutrition; IV, intravenous; WHO, World Health Organisation.

<sup>a</sup> AAP endorsement was published in *Pediatrics* 2004; 114(2): 507.

<sup>b</sup> Guarino *et al* (2008)

A number of surveys reviewed by Leung & Robson (2007) show that use of anti-emetics is widespread even without a formal recommendation for their use in paediatric gastroenteritis. Some physicians agree with the use of anti-emetics because vomiting is unpleasant and distressing for both child and parents and because vomiting can increase the likelihood of dehydration, electrolyte imbalance and the need for intravenous hydration and hospitalisation. Other physicians disagree with the use of anti-emetic medications because acute gastroenteritis is a self-limiting condition, vomiting might help rid the body of toxic substance, the relative lack of published evidence of clinical benefit and the potential adverse events associated with the use of anti-emetic medications.

## 9. Treatment details

The treatment details of anti-emetic medications used for managing acute gastroenteritis in children were reviewed by Freedman & Fuch (2004) and Leung & Robson (2007). The treatment details relating to metoclopramide, promethazine, domperidone and ondansetron are summarised in Table 4.

**Table 4: Treatment details of anti-emetic medications used for managing acute gastroenteritis in children**

	Min age	Max dose	IV (mg/kg)	IM (mg/kg)	Oral (mg/kg)	PR (mg/kg)
Metoclopramide	Not in neonates	10 mg	0.1	-	0.1	-
Promethazine	2 years	25 mg	0.25-1	0.25-1	0.25-1	0.25-1
Domperidone	None	80 mg	-	-	0.6	<2 yrs: 10 mg 2-6 yrs : 30 mg > 6years: 60 mg
Ondansetron	None	8 mg	0.1-0.5 <sup>a</sup>	-	8-15kg :2 mg 15-30kg: 4 mg >30 kg: 8 mg	-

Abbreviations: IM, intramuscular; IV, intravenous; PR, rectal administration

Source: Freedman & Fuchs (2004); Leung & Robson (2007); MARTINDALE<sup>®</sup> drug evaluations ([www.micromedex.com](http://www.micromedex.com)); WHO Model List of Essential Medicines for Children (October 2007).

<sup>a</sup> Maximum dose for IV administration is 4 mg

## 10. Identification of clinical evidence

Searches were conducted in the databases indicated in Table 5. The search terms included the following:

- Gastroenteritis, *and*
- Anti-emetic, metoclopramide, promethazine, domperidone, ondansetron

**Table 5: Electronic databases searched during the review of anti-emetics**

Database	Date Searched
MEDLINE and EMBASE <sup>a</sup>	19 June 2008
Cochrane library	19 June 2008
PREMEDLINE <sup>b</sup>	19 June 2008

<sup>a</sup> Using the EMBASE.com interface

<sup>b</sup> Using the PubMed interface

Comprehensive details of the literature searches performed using the electronic databases are presented in Appendix B. The citation lists of included studies were searched to identify any additional studies.

Studies were included for review if they were systematic reviews or randomised controlled trials (RCTs) evaluating the effectiveness of metoclopramide, promethazine, domperidone or ondansetron for the management of acute gastroenteritis in children.

Additional searches were conducted to source clinical guidelines and to identify potentially relevant trials in progress.

## 11. Summary of comparative effectiveness in a variety of clinical settings

### 11.1 Summary of available efficacy data

The literature search identified two relevant systematic reviews evaluating the effectiveness of anti-emetics in the management of acute gastroenteritis in children (Alhashimi *et al* 2006, Szajewska *et al* 2007).

An additional unpublished systematic review evaluating the safety and efficacy of domperidone and metoclopramide as anti-emetics in children was also reviewed as secondary evidence (Sri Ranganathan *et al*). The review identified five RCTs with 312 participants. Most of the studies were of poor methodological quality and conducted prior to 1980. The authors concluded that there is currently insufficient evidence regarding the safety and efficacy of metoclopramide and domperidone to determine their clinical value in children. It should be noted that the studies included in the review were not limited to acute gastroenteritis and included all studies of children with vomiting (except for chemotherapy-induced or post-operative nausea and vomiting.).

The literature search identified one relevant RCT that was excluded from both of the published systematic reviews (Van Eygen *et al* 1979). No comparative studies on promethazine were identified in the literature search.

Two studies evaluating the efficacy of ondansetron compared with placebo in acute viral gastritis (Stork *et al* 2006) or a mixed population of acute gastritis/gastroenteritis (Roslund *et al* 2007) were excluded from the current review. However it is probably worth noting that both of these studies reported results that favoured the use of ondansetron in the management of vomiting in their respective patient groups.

A brief search of [www.clinicaltrials.gov](http://www.clinicaltrials.gov) and [www.controlled-trials.com](http://www.controlled-trials.com) identified three potentially relevant trials that are still in-progress.

- NCT00120744, RCT of ondansetron vs placebo for children with acute gastroenteritis receiving oral rehydration therapy.
- NCT00124787, RCT of dimenhydrinate (an anti-histamine, same drug class as promethazine) vs placebo for children with acute gastroenteritis.
- NCT00691275, RCT of ondansetron vs placebo for children with acute gastroenteritis receiving IV rehydration therapy.

### *Systematic reviews*

The literature search identified two relevant systematic reviews; a broad review of anti-emetic medications for the management of acute gastroenteritis in children (Alhashimi *et al* 2006), and a more focused review evaluating the role of ondansetron (Szajewska *et al* 2007). Both systematic reviews examined a similar evidence base as the majority of the evidence regarding the use of anti-emetic medications for the management of acute gastroenteritis in children is based on ondansetron.

Despite some differences in the methodology used in each review, both systematic reviews were rated as high quality. The characteristics of the included systematic reviews are presented in Appendix C.

The two principal differences between the reviews were:

- The inclusion/exclusion status of the Reeves *et al* (2002) study  
Reeves *et al* (2002) was excluded from Alhashimi *et al* (2006) as the age of patients included in the trial ranged from 1 month to 22 years. However this study was included in the review by Szajewska *et al* (2007) as the mean age of the patient population was 5.3 years (standard deviation 4.9 years), this appears to be reasonable.
- The presentation of a meta-analysis  
A meta-analysis was not undertaken by Alashimi *et al* (2006) due to clinical heterogeneity between the included studies. In the meta-analysis of results by Szajewska *et al* (2007) no statistically significant heterogeneity was observed for the likelihood of vomiting cessation (soon after the administration of the intervention) and risk of requiring intravenous rehydration therapy. Significant heterogeneity was observed for all other outcomes.

The results and conclusions of each systematic review are presented in

Table 6. A summary of each of the studies included in the systematic reviews is shown in Table 7.

**Table 6: Results of systematic reviews assessing the effectiveness of anti-emetic medications**

Systematic review (year)	Results/conclusions
Alhashimi (2006)	<ul style="list-style-type: none"> <li>Descriptive analysis of Cubeddu (1997), Ramsook (2002) and Freedman (2006)</li> </ul> <p><b>Conclusion:</b> A weak body of evidence appears to favour the use of ondansetron or metoclopramide over placebo in the reduction of vomiting episodes associated with acute gastroenteritis in children.</p>
Szajewska (2007)	<ul style="list-style-type: none"> <li>Meta-analysis of Cubeddu (1997), Ramsook (2002), Reeves (2002) and Freedman (2006) <ul style="list-style-type: none"> <li>Ondansetron significantly increased the likelihood of vomiting cessation soon after the administration of the intervention (RR 1.33, 95% CI 1.19, 1.50; NNT 5) compared to placebo</li> <li>Ondansetron significantly reduced the risk of requiring intravenous rehydration therapy (RR 0.42, 95% CI 0.27, 0.67, NNT 7) compared to placebo</li> <li>There was no significant difference between ondansetron and placebo in the cessation of vomiting in 24 hours, the risk of hospitalisation or the need for a return visit to the emergency department.</li> <li>Most studies reported significantly more episodes of diarrhoea with ondansetron compared to placebo</li> </ul> </li> </ul> <p><b>Conclusion:</b> Ondansetron was associated with some clinical benefits however there is insufficient evidence to support the routine use of ondansetron in the management of vomiting associated with acute gastroenteritis in children</p>

Abbreviations: CI, confidence interval; NNT, number needed to treat; RR, relative risk

**Table 7: Summary of studies included in the systematic reviews**

Study	Study outline	Results/conclusions
Cubeddu (1997) Venezuela	<p>Double-blind RCT</p> <p>Patients aged 6 months – 8 years. All patients were hospitalised for 24 hours. (N = 12)</p> <p><b>Ondansetron:</b> Single dose, IV injection 0.3 mg/kg</p> <p><b>Metoclopramide:</b> Single dose, IV injection 0.3 mg/kg</p> <p><b>Placebo</b></p> <p>Anti-emetic therapy administered concurrently with ORT (WHO recommended ORS)</p>	<ul style="list-style-type: none"> <li>Ondansetron was significantly superior to placebo in preventing vomiting</li> <li>No statistically significant difference between metoclopramide and placebo</li> <li>More diarrhoeal episodes were observed in patients treated with ondansetron or metoclopramide compared to placebo</li> <li>There was no significant difference in the adverse events for ondansetron or metoclopramide compared to placebo</li> </ul>
Ramsook (2002) USA	<p>Double-blind RCT</p> <p>Patients aged 6 months – 12 years. (N = 145)</p> <p><b>Ondansetron:</b> Six doses, oral solution 1.6-4 mg based on age</p> <p><b>Placebo</b></p> <p>Anti-emetic therapy administered concurrently with ORT (Pedialyte® ORS)</p>	<ul style="list-style-type: none"> <li>Ondansetron was significantly superior to placebo in reducing vomiting in the emergency department and in lowering the rates of intravenous fluid administration and hospital admission.</li> <li>Significantly more diarrhoeal episodes were observed over 48 hours in patients treated with ondansetron compared to placebo</li> <li>Children who received ondansetron were more likely to return to the emergency department</li> </ul>

Study	Study outline	Results/conclusions
Reeves (2002)  USA	Double-blind RCT  Patients aged 1 month – 22 years. (N = 107) <b>Ondansetron:</b> Single dose, IV injection 0.15 mg/kg (maximum 8 mg) <b>Placebo</b>  Anti-emetic therapy administered concurrently with IV replacement therapy	- Ondansetron was significantly superior to placebo in preventing vomiting - No significant difference between treatment groups for diarrhoea-related outcomes - There was no significant difference in the adverse events reported for ondansetron compared to placebo
Freedman (2006)  Canada	Double-blind RCT  Patients aged 6 months – 10 years. (N = 214) <b>Ondansetron:</b> Single dose, disintegrating tablet 2-8 mg based on body weight <b>Placebo</b>  Anti-emetic therapy administered concurrently with ORT (Enfalyte® ORS)	- Ondansetron was significantly superior to placebo in reducing vomiting, facilitating ORT and in lowering the rates of intravenous fluid administration. - Significantly more diarrhoeal episodes were observed in patients treated with ondansetron compared to placebo - There was no significant difference in the adverse events reported for ondansetron compared to placebo

Abbreviations: IV, intravenous; ORS, oral replacement solution; ORT, oral replacement therapy; RCT, randomised controlled trial; WHO, World Health Organisation.

All the studies included in the systematic reviews reported results in favour of ondansetron treatment. The study by Cubeddu et al (1997) showed no significant benefit of metoclopramide over placebo. The included studies also reported an increase in diarrhoea episodes associated with use of anti-emetic medications.

Both systematic reviews highlighted the limitations of the current body of evidence, including the small number of patients evaluated; the methodological limitations of the included studies (primarily poor reporting) and the differences in study characteristics (patient populations, administered interventions and outcome definitions).

Based on the studies evaluated in the systematic reviews there is some evidence supporting the effectiveness of ondansetron (when used concomitantly with rehydration therapy) but the body of evidence is insufficient to recommend the routine use of anti-emetic medications.

#### *Randomised controlled trials*

The literature search identified one relevant RCT (Van Eygen *et al* 1979) (summarised in

Table 8). This study was excluded from the systematic review by Alhashimi *et al* (2006) as it did not report on any of the primary or secondary outcomes of the review. This study was also not relevant to the review of ondansetron by Szajewska *et al* (2007).

**Table 8: Summary of Van Eygen et al (1979) study**

Study	Study outline	Results/conclusions
Van Eygen (1979) Belgium	Double-blind RCT Patients aged 2 – 6 years. (N = 60) <b>Domperidone:</b> Up to four doses as required. 30 mg suppository <b>Metoclopramide:</b> Up to four doses as required. 10 mg suppository <sup>a</sup> <b>Placebo</b> Unclear reporting on the use of rehydration therapies	- Domperidone was significantly superior to placebo and metoclopramide in reducing the severity of vomiting, nausea and other symptoms of gastroenteritis. - Metoclopramide was significantly superior to placebo in reducing the symptoms of gastroenteritis - There were no side effects reported during the trial

Abbreviations: RCT, randomised controlled trial

<sup>a</sup> Metoclopramide as a suppository is not a formulation considered for listing on the WHO essential medicines list for children.

The study by Van Eygen et al (1979) reported that both metoclopramide and domperidone reduced the severity of gastroenteritis symptoms compared to placebo. Since this study was conducted there have been improvements in the management of children with gastroenteritis (eg changes in the use of ORT) and it is unlikely that the results of this study would be applicable to current clinical practice.

## 11.2 Summary of available safety data

The limited safety data available from comparative efficacy trials indicate that anti-emetic medications are associated with significantly more episodes of diarrhoea. The number of patients enrolled in the comparative trials was too small to appropriately establish the risk profile of anti-emetics in children with acute gastroenteritis.

Leung & Robson (2007) reviewed the results from physician surveys and studies reporting on anti-emetic prescription patterns in children with acute gastroenteritis. The authors concluded on the basis of these results that anti-emetic medication use among children with acute gastroenteritis is common and that adverse events are uncommon.

Adverse events associated with metoclopramide, promethazine, domperidone and ondansetron are listed below (MARTINDALE<sup>®</sup> evaluations [www.micromedex.com](http://www.micromedex.com), MIMS<sup>®</sup> Australia <http://www.mims.com.au>)

It should be noted that one of the reasons why the WHO guidelines recommend against using anti-emetic medications is their potential to cause sedation which increases the difficulty of administering ORT (WHO, 2005)

### Metoclopramide

- The most frequently reported adverse events include restlessness, drowsiness, fatigue and lassitude.
- Uncommon adverse events include insomnia, headache, dizziness, nausea, or bowel disturbances.
- Rare adverse events include acute depression, anxiety or agitation.
- Very rare adverse events include neuroleptic malignant syndrome.
- Reports of hypertension, hypotension, supraventricular tachycardia and cardiac conduction defects have been associated with metoclopramide.

- Metoclopramide stimulates prolactin secretion
- Haematological disorders, hyperprolactinaemia, galactorrhoea, mastodynia and aldosteronism have also been reported.
- Metoclopramide has been associated with extrapyramidal effects due to its dopamine antagonism action. These effects include dystonic reactions (more common in children and young adults and at daily doses greater than 500 mcg/kg). The majority of these symptoms are self-limiting however close observation is required.
- Metoclopramide has also been associated with drug-induced Parkinsonism and tardive dyskinesias in elderly patients.

### **Promethazine**

- More common reactions include dry mouth, epigastric distress, loss of appetite, nausea, vomiting, constipation, diarrhoea, sedation, restlessness, dizziness, lassitude, incoordination, fatigue and blurred vision.
- Less common reactions include tachycardia, bradycardia, faintness, contact dermatitis (topical), photosensitisation, urticaria, angioneurotic oedema, pruritus leucopenia, agranulocytosis, aplastic anaemia, thrombocytopenic purpura, jaundice, extrapyramidal symptoms, tinnitus, euphoria, nervousness, insomnia, convulsive seizures, oculogyric crises, excitation, catatonic-like states, hysteria, tardive dyskinesia, marked irregular respiration.
- Severe reactions include agranulocytosis, anaphylaxis and respiratory depression.
- Promethazine has been associated with CNS depressive effects (eg sedation and impaired performance)
- Promethazine had also been associated with CNS stimulatory effects (eg anxiety, hallucinations, appetite stimulation, muscle dyskinesias and activation of epileptogenic foci)
- High doses of promethazine may increase likelihood of nervousness, tremor, insomnia, agitation and irritability.
- Promethazine is not recommended for children less than two years of age due to the potential for fatal respiratory depression.

### **Domperidone**

- More common events include dry mouth and headache
- Less common events include insomnia, nervousness, dizziness, thirst, lethargy, irritability, abdominal cramps, diarrhoea, regurgitation, changes in appetite, nausea, heartburn, constipation, rash, pruritus, urticaria, urinary frequency, dysuria, oedema, palpitations, leg cramps, asthenia, conjunctivitis, stomatitis, drug intolerance.
- Rare adverse events include extrapyramidal reactions (more common in children than adults), amenorrhoea, galactorrhoea, gynaecomastia.
- Very rare adverse events include angioedema and anaphylactic reaction (eg anaphylactic shock)
- Domperidone stimulates prolactin secretion. Also elevates AST, ALT and cholesterol levels
- Long-term domperidone use has been associated with events possibly related to prolactin secretion (eg gynaecomastia, breast tenderness, swelling of the breasts, irregular menses, amenorrhoea, a decrease or loss of libido, breast secretion and lactation)

- Intravenous domperidone is not recommended for children due to the potential for QTc prolongation, ventricular arrhythmia and sudden death with this formulation.

### **Ondansetron**

- The most frequently reported adverse events include headache
- Common adverse events include sensation of warmth or flushing, constipation, xerostomia, injection site reactions
- Uncommon adverse events include seizures, movement disorders (including extrapyramidal reactions), arrhythmias, chest pain with or without ST segment depression, bradycardia, hypotension, hiccups, asymptomatic increases in liver function tests.
- Rare adverse events include immediate hypersensitivity reactions (eg anaphylaxis), dizziness, blurred vision,
- Very rare adverse events include transient blindness

### **11.3 Discussion**

The current body of evidence is insufficient to recommend the routine use of anti-emetics in the management of children with gastroenteritis.

There is little evidence supporting the efficacy of dopamine antagonists (metoclopramide, domperidone) or anti-histamines (promethazine) in reducing vomiting in children with gastroenteritis. This is in contrast with known adverse events associated with these drugs including extrapyramidal symptoms and sedation.

While routine administration of anti-emetic medications cannot be recommended, serotonin 5-HT<sub>3</sub> antagonists (ondansetron) may be a useful treatment option on a case-by-case basis.

## **12. Summary of available data on comparative cost and cost effectiveness within the pharmacological class or therapeutic group**

### **12.1 Global costs of anti-emetics**

The prices of metoclopramide, promethazine and ondansetron published in the International Drug Price Indicator Guide ([www.erc.msh.org](http://www.erc.msh.org)) are summarised in

Table 9. The pricing details for other formulations of metoclopramide, promethazine and ondansetron were not reviewed.

Domperidone is not currently listed in the international drug price indicator guide however Australian pricing details are available ([www.mims.com.au](http://www.mims.com.au), prices in Australian dollars): 10 mg tablets (25 pack): \$7.81; 10 mg tablets (100 pack): \$24.65. Pricing details for other formulations of domperidone were not reviewed.

**Table 9: Cost of anti-emetic medications listed on the International Drug Price Indicator Guide**

	<b>Formulation, Strength</b>	<b>Median supplier price<sup>a</sup></b>	<b>Median buyer price<sup>a</sup></b>
Metoclopramide	Injection 5 mg/mL	\$0.0450/mL	\$0.0777/mL
	Tablets 10 mg	\$0.0044/tablet	\$0.0072/tablet
	Oral liquid 5 mg/5 mL	-	\$0.0104/mL
	Drops 4 mg/mL	\$0.0314/mL	-
Promethazine	Injection 25 mg/mL	\$0.0702/mL	\$0.0633/mL
	Tablets 25 mg	\$0.0037/tablet	\$0.0042/tablet
	Oral liquid 5 mg/5 mL	\$0.0060/mL	\$0.0021/mL
Ondansetron	Injection 2 mg/mL	-	\$2.0194/mL
	Tablets 4 mg	-	\$2.0284/tablet
	Tablets 8 mg	-	\$7.6716/tablet

Source: International Drug Price Indicator Guide ([www.erc.msh.org](http://www.erc.msh.org))

<sup>a</sup> Price in US dollars

It is likely that the price of ondansetron will continue to change as it has only recently become available as a generic medicine.

Two examples are presented below in order to assist in the interpretation of the costing data.

- The study by Cubeddu et al (1997) used a 0.3 mg/kg IV injection of metoclopramide. Even based on the heaviest child treated with metoclopramide (23 kg), the dose required would have been less than the minimum dispensed volume (ampoule 2mL). Using the prices reported in

Table 9 the minimum dispensed volume would have cost approximately 10 cents. However this does not include the cost of IV administration.

- The study by Freedman et al (2006) treated children with ondansetron tablets based on the body weight of patients. An 8mg dose was the highest dose administered (to children weighing > 30 kg). Using the prices reported in

Table 9 this would have cost approximately US\$8 dollars. However the majority of the patients in this trial weighed considerably less and would have been treated with a 2-4mg dose of ondansetron.

## 12.2 Cost effectiveness

No studies were identified that examined the cost-effectiveness of anti-emetic medications for the management of acute gastroenteritis in children.

## 13. Summary of regulatory status of the medicine

Anti-emetic medications (dopamine agonists, anti-histamines and serotonin 5-HT<sub>3</sub> antagonists) have not been registered with regulatory agencies for the treatment of acute gastroenteritis in children.

Indications for metoclopramide, promethazine, domperidone and ondansetron are listed below (DRUGDEX<sup>®</sup> evaluations [www.micromedex.com](http://www.micromedex.com), MIMS<sup>®</sup> Australia <http://www.mims.com.au>)

**Metoclopramide:** *Adult:* Nausea and vomiting from any cause (except motion sickness), diabetic gastroparesis, gastroesophageal reflux disease, small bowel intestinal intubation, gastric retention after surgery, facilitate absorption of other drugs, adjunct to radiography of the gastrointestinal tract. *Child:* Small bowel intestinal intubation, severe intractable vomiting of known cause, chemotherapy-induced nausea and vomiting, post-operative nausea and vomiting.

**Promethazine:** *Adult:* Treatment of allergies, adjunct to anaesthesia, motion sickness; nausea and vomiting from any cause, adjunct to management of post-operative pain, general sedation, obstetric sedation. *Child:* Treatment of allergies, treatment and prophylaxis for motion sickness, nausea and vomiting of known cause, adjunct to management of post-operative pain, general sedation.

**Domperidone:** *Adult:* Treatment of postprandial indigestion, migraine, restless legs syndrome, idiopathic/diabetic gastroparesis, acute nausea and vomiting from any cause. *Child:* Prophylaxis for chemotherapy-induced nausea and vomiting.

**Ondansetron:** *Adult:* Chemotherapy-induced nausea and vomiting, post-operative nausea and vomiting. *Child:* Chemotherapy-induced nausea and vomiting, post-operative nausea and vomiting

## 14. Availability of pharmacopoeial standards

From MARTINDALE<sup>®</sup> database ([www.micromedex.com](http://www.micromedex.com))

*Metoclopramide:* Chinese, European and Japanese pharmacopoeias

*Metoclopramide hydrochloride:* European, US and international pharmacopoeias

*Promethazine hydrochloride:* Chinese, European, Japanese, Vietnamese, US and international pharmacopoeias

*Promethazine teoclate:* British pharmacopoeia

*Domperidone:* European pharmacopoeia

*Domperidone maleate:* European pharmacopoeia

*Ondansetron:* US pharmacopoeia

*Ondansetron hydrochloride*: Chinese, European and US pharmacopoeias

**15. Proposed text for the WHO Model Formulary**

Dopamine agonists, anti-histamines and serotonin 5-HT<sub>3</sub> antagonists have not been registered with regulatory agencies for the treatment of acute gastroenteritis in children. Additionally the current body of evidence is insufficient to recommend the routine use of anti-emetics in the management of children with gastroenteritis. Therefore a proposed formulary text has not been presented.

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**Appendix A**

A review of the MARTINDALE® database was undertaken to identify common brand names for domperidone, metoclopramide, ondansetron and promethazine (summarised in Table A. 1).

**Table A. 1 Common brand names for domperidone, metoclopramide, ondansetron and promethazine**

<b>INN</b>	<b>Common brand names</b>
Domperidone	Aciloc RD, Agilam, Alplax Net, Anselix Digest, Bigetric, Bilagol, Biolix, Biperidys, Cilroton, Cinet, Costi, Dany, Digestivo Giuliani, Docdomperi, Dolium, Domcet, Domerdon, Domidone, Domilium, Dompel, Dompenny, Dompeon, Domper, Domperdone, Domperi, Domperitop, Domperol, Domperon, Dom-Polienzim, Domstal, Donegal, Donum, Doridone, Doridone, Dosin, Ecuamon, Emiken, Esoz-D, Euciton, Euciton Complex, Euciton Reflux, Euciton Stress, Evoxin, Faradil Novo, Fobidon, Gasdol, Gastronorm, Gilax, Idon, Megalex, Mirax, Mocydone, Mod, Modomed, Mogasinte, Molax, Moperidona, Moperidona AF, Moperidona Enzimatica, Moticon, Motidom, Motilak, Motilium, Motilyo, Motonium, Movelim, Nautigo, Nauzelin, Ninlium, Nogacid D, Nordonil, Okacid D, Okalan D, Pantosec D, Passagix, Peptomet, Peridal, Peridon, Peridon, Peridys, Permod, Pleiadon, Pondperdone, Poselium, Praize-D, Praxis, Qualidom, Rabugen, Remotil, Restol, Riges, Seronex, Sidomal, Siligaz, Stalcare, Stopvom, Tensium Gastric, Tetralgin Novo, Tilium, Tonun, Vegestabil Digest, Vertigil, Vomidon, Vomistop
Metoclopramide	Aeroflat, Aerogastrol, Aero Itan, Afipran, Anagraine, Antigram, Biopram, Bitecain AA, Celit, Ceolat compositum, Cirulan, Clodoxin, Clop, Clopamon, Clopra, Dart, Digesplen, Digest, Docmetoclo, Dolmisiin, Ede, Emetic, Emetrol, Estomaplus, Eudiges, Eugastran, Facilgest, Factorine, Faradil, Faradil Enzimatico, Fonderyl, Garceptol, Gastronerton, Gastrosil, Gastrosindrom, Gensil, Hawkperan, Hopram, H-Peran, Hyrin, Ibsesal, Irtoipan, Itan, Kilozim, Lizarona, Maxolon, MCP, Metoc, Midatenk, Mipramid, Mosil Complex, Nausil, No-Ref, No-Vomit, Novomit, Paidozim, Pakinase, Pangastren, Paramet, Peremid, Plagon, Plasil, Pradamin, Pramide, Pramil, Pramilem, Pramotil, Prael, Premieran, Primoxan, Primperan, Primperan Complex, Primperil, Primperoxane, Propace, Reliveran, Rupemet, Sintegran, Surifarm, Tetralgin, Timulcer, Vibralen, Vominil, Vominorm, Vomistop, Vomix, Vonifin, Vonil Enzimatico
Ondansetron	Amilene, Atossa, Biosetron, Cetron, Cruzafen, Dantron, Dentron, Dismolan, Emivox, Espasevit, Fedral, Finoxi, Gardoton, Glaxosetron, Izofran, Odanex, Odnatron, Onda, Ondameton, Ondanoglax, Ondansetron Orally Disintegrating Tablets USP 29, Ondaseprol, Ondaz, Ondemet, Precirux, Setrodan, Trorix, Tructum, Vefron, Zetron, Zodatron, Zofer, Zofran, Zophralen, Zophren
Promethazine	Alergosan, Atosil, Boipulmonale Simple, Crema Anitallergica Antipruriginosa, Diven, Doriless, Fargan, Fenegan, Fenegan Topico, Lisador, PCL, Phenergan, Phenergan Expectorant, Promedyl, Prometazol, Promethegan, Rectoquintyl-Promethazine, Tussisedal

Source: MARTINDALE® drug evaluations ([www.micromedex.com](http://www.micromedex.com))

## **Appendix B**

Search strategies were used to identify relevant studies of anti-emetics for the management of acute gastroenteritis in children. The MEDLINE and EMBASE databases were search using the EMBASE.com interface. The PREMEDLINE database was search using the PUBMED interface. The CDSR, DARE, CENTRAL, CMR, HTA, NHSEED databases were search using the Cochrane library interface. The search results for EMBASE.com are presented in Table B. 1, the results of the Cochrane library are presented in Table B. 2 and the results from PUBMED are presented in

Table B. 3.

**Table B. 1: Anti-emetics for the management of acute gastroenteritis in children.  
EMBASE.com search strategy (19<sup>th</sup> June 2008)**

#	Keywords	Results
1	'gastroenteritis'/exp	11,355
2	'gastroenteritis':ti,ab OR 'gastro enteritis':ti,ab OR 'gastroduodenitis':ti,ab OR 'gastrointestinal acute infection':ti,ab	10,978
3	#1 OR #2	16,371
4	'antiemetic agent'/exp	120,828
5	'anti emetic':ti,ab OR 'antiemetic':ti,ab OR 'anti-emetic':ti,ab	4,514
6	'metoclopramide'/exp	17,391
7	('4 amino 5 chloro n (2 diethylaminoethyl) 2 methoxybenzamide':ti,ab OR '4 amino 5 chloro n (2 diethylaminoethyl) o anisamide':ti,ab OR '4 amino 5 chloro n (2 diethylaminoethyl) ortho anisamide':ti,ab OR '5 chloro 2 methoxyprocainamide':ti,ab OR 'ahr 3070 c':ti,ab OR 'ahr 3070c':ti,ab OR 'ahr3070c':ti,ab OR 'cerucal':ti,ab OR 'clodilion':ti,ab OR 'clopra':ti,ab OR 'del 1267':ti,ab OR 'del1267':ti,ab OR 'dibertil':ti,ab OR 'duraclamid':ti,ab OR 'emenil':ti,ab OR 'emetard':ti,ab OR 'emitasol':ti,ab OR 'encil':ti,ab OR 'gastro timelets':ti,ab OR 'gastrobid':ti,ab OR 'gastrobid continus':ti,ab OR 'gastronerton':ti,ab OR 'gastrosil':ti,ab OR 'gastrotem':ti,ab OR 'gastrotimelets':ti,ab OR 'hyrin':ti,ab OR 'm 813':ti,ab OR 'm813':ti,ab OR 'maxeran':ti,ab OR 'maxeron':ti,ab OR 'maxolan':ti,ab OR 'maxolon':ti,ab OR 'meclopamide':ti,ab OR 'meclopramide':ti,ab OR 'meclopran':ti,ab OR 'metaclopramide':ti,ab OR 'methochlopramide':ti,ab OR 'methoclopramide':ti,ab OR 'methoclopramine':ti,ab OR 'metochlopramide':ti,ab OR 'metoclopramid':ti,ab OR 'metoclopramide chlorhydrate':ti,ab OR 'metoclopramide dihydrochloride':ti,ab OR 'metoclopramide hydrochloride':ti,ab OR 'metoclopramide monohydrochloride monohydrate':ti,ab OR 'metoclopramide with polidocanol':ti,ab OR 'metoclopramine':ti,ab OR 'metoclopranide hydrochloride':ti,ab OR 'metoclorpramide':ti,ab OR 'metodopramide':ti,ab OR 'metopram':ti,ab OR 'metox':ti,ab OR 'metpamid':ti,ab OR 'mygdalon':ti,ab OR 'neu sensamide':ti,ab OR 'octamide':ti,ab OR 'paspertin':ti,ab OR 'paspertin retard':ti,ab OR 'perinorm':ti,ab OR 'plasil':ti,ab OR 'pramidin':ti,ab OR 'pramin':ti,ab OR 'primperan':ti,ab OR 'reclomide':ti,ab OR 'reglan':ti,ab OR 'reglan injectable':ti,ab OR 'rimetin':ti,ab OR 'sensamide':ti,ab OR 'tomid':ti,ab OR 'metoclopramide':ti,ab)	5,642

#	Keywords	Results
8	'promethazine'/exp	10,156
9	('10 (2 dimethylaminopropyl) phenothiazine':ti,ab OR 'allergan':ti,ab OR 'anergan 25':ti,ab OR 'anergan 50':ti,ab OR 'antiallersin':ti,ab OR 'atosil':ti,ab OR 'baymethazine':ti,ab OR 'dimapp':ti,ab OR 'diprazin':ti,ab OR 'diprazine':ti,ab OR 'diprozin':ti,ab OR 'fargan':ti,ab OR 'fellozine':ti,ab OR 'fenazil':ti,ab OR 'fenergan':ti,ab OR 'ganphen':ti,ab OR 'hiberna':ti,ab OR 'lercigan':ti,ab OR 'lergigan':ti,ab OR 'n (2 dimethylaminopropyl) phenothiazine':ti,ab OR 'phargan':ti,ab OR 'phenergan':ti,ab OR 'phenergan expectorant':ti,ab OR 'phensedyl':ti,ab OR 'pipolphen':ti,ab OR 'pm 284':ti,ab OR 'proazamine':ti,ab OR 'procit':ti,ab OR 'promazinamide':ti,ab OR 'promethacin':ti,ab OR 'promethazin':ti,ab OR 'promethazine calcium':ti,ab OR 'promethazine hcl':ti,ab OR 'promethazine hydrochloride':ti,ab OR 'promethazone':ti,ab OR 'protazine':ti,ab OR 'prothazine':ti,ab OR 'provigan':ti,ab OR 'pyrethia':ti,ab OR 'remsed':ti,ab OR 'romergan':ti,ab OR 'rp 3277':ti,ab OR 'rp 3389':ti,ab OR 'sayomol':ti,ab OR 'tanidil':ti,ab OR 'thiergan':ti,ab OR 'vallergine':ti,ab OR 'promethazine':ti,ab)	2,251
10	'domperidone'/exp	5,810
11	('4 (5 chloro 2 oxobenzimidazolin 1 yl) 1 [3 (2 oxobenzimidazolin 1 yl) propyl] piperidine':ti,ab OR '5 chloro 1 [1 [3 (2 oxo 1 benzimidazoliny) propyl] piperid 4 yl] 2 benzimidazolinone':ti,ab OR 'kw 5338':ti,ab OR 'motilium':ti,ab OR 'peridon':ti,ab OR 'peridys':ti,ab OR 'r 33':ti,ab OR '812':ti,ab OR 'r 33812':ti,ab OR 'domperidone':ti,ab)	4,095
12	'ondansetron'/exp	8,398
13	('1, 2, 3, 9 tetrahydro 3 [(2 methylimidazol 1 yl) methyl] 9 methyl 4h carbazol 4 one':ti,ab OR '1, 2, 3, 9 tetrahydro 9 methyl 3 [(2 methyl 1h imidazol 1 yl) methyl] 4h carbazol 4 one':ti,ab OR 'ceramos':ti,ab OR 'gr 38032':ti,ab OR 'gr 38032f':ti,ab OR 'gr c507 75':ti,ab OR 'gr38032':ti,ab OR 'gr38032f':ti,ab OR 'odansetron':ti,ab OR 'ondansetron hydrochloride':ti,ab OR 'sn 307':ti,ab OR 'zofran':ti,ab OR 'zofran odt':ti,ab OR 'zofrene':ti,ab OR 'zophran':ti,ab OR 'zophren':ti,ab OR 'ondansetron':ti,ab)	2,820
14	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	125,402
15	#3 AND #14	207

**Table B. 2: Anti-emetics for the management of acute gastroenteritis in children, Cochrane library search strategy (19<sup>th</sup> June 2008, Issue 2)**

#	Keywords	Results
1	MeSH descriptor Gastroenteritis explode all trees	3,395
2	"gastroenteritis" or "gastro enteritis" or "gastro-enteritis"	417
3	(#1 OR #2)	3,582
4	MeSH descriptor Antiemetics explode all trees	9,369
5	MeSH descriptor Metoclopramide explode all trees	889
6	MeSH descriptor Promethazine explode all trees	210
7	MeSH descriptor Domperidone explode all trees	151
8	MeSH descriptor Ondansetron explode all trees	758
9	"anti emetic" or "antiemetic" or "anti-emetic" or "metoclopramide" or "promethazine" or "domperidone" or "ondansetron"	4,438
10	(#4 OR #5 OR #6 OR #7 OR #8 OR #9)	11,483
11	(#3 AND #10)	80

**Table B. 3: Anti-emetics for the management of acute gastroenteritis in children, Pubmed search strategy (19<sup>th</sup> June 2008)**

#	Keywords	Results
1	"gastroenteritis" [tiab] OR "gastro enteritis" [tiab] OR "gastro-enteritis" [tiab]	9881
2	"anti emetic" [tiab] OR "antiemetic" [tiab] OR "anti-emetic" [tiab]	4041
3	metoclopramide [tiab]	4591
4	promethazine [tiab]	1637
5	domperidone [tiab]	1669
6	ondansetron [tiab]	2522
7	#2 or #3 or #4 or #5 or #6	12255
8	#1 and #7	35
9	#1 and #7 Limits: MEDLINE	31
10	#8 NOT #9	4

## Appendix C

Two systematic reviews were identified that assessed the evidence for the use of anti-emetics in the management of children with acute gastroenteritis. The characteristics of these reviews are summarised in Table C. 1.

**Table C. 1: Characteristics of systematic reviews assessing the effectiveness of anti-emetic medications**

Systematic review (year)	Search Strategy	Inclusion criteria (included studies)	Methodology	Comment
Alhashimi (2006)	<p>A literature search was conducted using Medline, Embase and Cochrane databases. Reference lists of included articles were searched. Communication with experts to identify unpublished studies</p> <p>Detailed search strategy. Search terms included terms for gastroenteritis combined with terms for anti-emetics</p> <p>Literature search was originally conducted in July 2005, the search was updated in July 2006</p>	<p>Studies with the following characteristics were included: RCT, diagnosis of gastroenteritis, patients &lt;18 years of age</p> <p>(n = 3)</p>	<p>The literature review and data extraction were completed by two independent reviewers</p> <p>An assessment of quality (randomisation, blinding, allocation concealment) was undertaken</p> <p>Results were not meta-analysed</p>	High quality
Szajewska (2007)	<p>A literature search was conducted using Medline, Embase, CINAHL and Cochrane databases. Reference lists of included articles were searched.</p> <p>Brief search strategy. Keywords included "ondansetron, diarrhoea, gastroenteritis, vomit"</p> <p>Literature search conducted in August 2006</p>	<p>Studies with the following characteristics were included: RCT, children with a diagnosis of gastroenteritis, comparison between ondansetron and placebo (or no intervention)</p> <p>(n = 4)</p>	<p>The literature review and data extraction were completed by two independent reviewers</p> <p>An assessment of quality (randomisation, blinding, allocation concealment) was undertaken</p> <p>A meta-analysis was conducted using fixed and random effects models. Cochran Q and I<sup>2</sup> index used to test heterogeneity. Binary outcomes were presented as RR and NNT. Continuous outcomes were presented as WMD</p>	High quality

Abbreviations: CINAHL, Cumulative Index to Nursing and Allied health; NNT, number needed to treat; RCT, randomised controlled trial; RR, relative risk; WMD, weighted mean difference.