Management of vomiting in children and young people with gastroenteritis: ondansetron

Evidence summary

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Key points from the evidence

> The content of this evidence summary was up-to-date in October 2014. See summaries of product characteristics (SPCs), British national formulary (BNF), BNF for children (BNFc) or the MHRA or NICE websites for up-to-date information.

Summary

A Cochrane review of antiemetic treatment for children and young people with acute gastroenteritis found oral or intravenous ondansetron increased the proportion of children and young people who stopped vomiting compared with placebo. Oral ondansetron also reduced the proportion of children and young people needing intravenous fluid therapy and reduced the immediate hospital admission rate compared with placebo. Ondansetron was associated with increased episodes of diarrhoea.

Regulatory status: off-label. This topic was prioritised because there was a high volume of requests from the NHS. In 2009, the guideline development group for the NICE clinical guideline on diarrhoea and vomiting caused by gastroenteritis: diagnosis, assessment and management in children younger than 5 years concluded that administration of antiemetics could not currently be recommended. However, further research on the use of ondansetron was needed, focusing particularly on the possible risk of worsened diarrhoea. This evidence summary reviews the evidence that is now available to support decision-making in this area, but this summary is not NICE guidance.

Effectiveness	Safety
A Cochrane review of antiemetic treatment for children and young people with acute gastroenteritis found: • oral ondansetron increased the proportion of children and young people who stopped vomiting compared with placebo (relative risk [RR] 1.44, 95% CI 1.29 to 1.61, p<0.00001, number needed to treat [NNT] 4; 4 RCTs [n=574]) • oral ondansetron reduced the proportion of children and young people needing intravenous fluid therapy compared with placebo (RR 0.41, 95% CI 0.29 to 0.59, p<0.00001, NNT 5; 3 RCTs [n=465]) • oral ondansetron reduced the immediate hospital admission rate compared with placebo (RR 0.40, 95% CI 0.19 to 0.83, p=0.01; 3 RCTs [n=465]) • intravenous ondansetron increased the proportion of children and young people who stopped vomiting compared with placebo (RR 2.01, 95% CI 1.49 to 2.71, p<0.00001, NNT 3; 3 RCTs [n=186]).	• Ondansetron prolongs the QT interval in a dose-dependent manner. It should be avoided in people with congenital long QT syndrome and used with caution in people who have or may develop prolongation of QTc, such as those with electrolyte abnormalities, congestive heart failure, bradyarrhythmias or people taking other medicinal products that lead to QT prolongation or electrolyte abnormalities. Hypokalaemia and hypomagnesaemia should be corrected prior to ondansetron administration (July 2013 Drug Safety Update and ondansetron summaries of product characteristics).

Patient factors	Resource implications
• A Cochrane review found oral and intravenous ondansetron increased the number of episodes of diarrhoea compared with placebo (p<0.05). • For children and young people who are unable to swallow tablets, oral ondansetron can be given as an orodispersible tablet which is placed on top of the tongue or as an oral solution.	• Ondansetron tablets are £1.71 for 10×4 mg tablets, and £44.05 for 10×8 mg tablets (excluding VAT; Drug Tariff, September 2014). • Ondansetron orodispersible tablets are £35.97 to £37.76 for 10×4 mg tablets and £71.94 to £75.53 for 10×8 mg tablets (excluding VAT; Drug Tariff, September 2014). • Ondansetron 4 mg/5 ml oral solution is £36.82 for 50 ml (excluding VAT; Drug Tariff, September 2014). • Ondansetron (Zofran) 2 mg/ml injection is £29.97 for 5×2 ml (4 mg) ampoules and £59.95 for 5×4 ml (8 mg) ampoules (excluding VAT; MIMS September 2014).

Introduction and current guidance

NICE published a clinical guideline on diarrhoea and vomiting caused by gastroenteritis: diagnosis, assessment and management in children younger than 5 years in 2009. The management of gastroenteritis in children is multifaceted, and this guideline covers diagnosis, assessment of dehydration and shock, fluid management, nutritional management and the role of antibiotics and other therapies.

The evidence for the use of antiemetics was reviewed in the full NICE guideline. After reviewing this evidence, the guideline development group concluded that oral ondansetron could increase the success rate with oral rehydration therapy (thereby reducing the need to treat with intravenous fluid therapy), but there was a concern that it might worsen diarrhoea. There was no evidence to support other agents, including metoclopramide and dexamethasone. The guideline development group concluded that administration of antiemetics could not currently be recommended, but further research on the use of

ondansetron was needed.

Full text of Introduction and current guidance.

Product overview

Ondansetron is a potent, highly selective 5HT3 receptor antagonist. It is licensed for use in children and young people for the management of chemotherapy-induced nausea and vomiting and for the prevention and treatment of post-operative nausea and vomiting (see individual summaries of product characteristics for details).

Ondansetron is not licensed for the management of vomiting in children and young people with gastroenteritis, therefore using it for this indication is off-label.

Full text of Product overview.

Evidence review

This evidence summary is based on the evidence review of antiemetics for the full NICE guideline on diarrhoea and vomiting caused by gastroenteritis in children younger than 5 years published in 2009, an updated Cochrane review of antiemetics for acute gastritis in children and young people (Carter and Fedorowicz 2012) and a retrospective cohort study of ondansetron use in the emergency departments of children's hospitals in the USA (Freedman et al. 2014).

- The updated Cochrane review (Carter and Fedorowicz 2012) included 10 randomised controlled trials (RCTs; n=1479) in children and young people aged 3 months to 13 years. Four of the included RCTs investigated oral ondansetron, 4 RCTs investigated intravenous ondansetron, 1 RCT investigated a dimenhydrinate suppository and 1 investigated oral granisetron.

- Dosing regimens varied between the 8 RCTs which investigated ondansetron but most used a weight-dependent dosage. In most studies a single oral or intravenous dose of ondansetron was given. Oral ondansetron (2 mg to 8 mg depending on weight or age) was given as an orodispersible tablet or a solution, and intravenous ondansetron was mainly given at a dose of 0.15 mg/kg (0.3 mg/kg in 1 study).

- Pooled data from 4 RCTs (n=574) found oral ondansetron was more effective than placebo at stopping vomiting based on the proportion of children and young people who stopped vomiting (relative risk [RR] 1.44, 95% confidence interval [CI] 1.29 to 1.61, p<0.00001, number needed to treat [NNT] 4 [95% CI 4 to 6]).

- Pooled data from 3 RCTs (n=465) found the proportion of children and young people needing intravenous fluid therapy was lower with oral ondansetron compared with placebo during the emergency department stay (RR 0.41, 95% CI 0.29 to 0.59, p<0.00001, NNT 5 [95% CI 4 to 8]) and up to 72 hours after discharge.

- Pooled data from 3 RCTs (n=465) found oral ondansetron reduced the immediate hospital admission rate during the emergency department stay (RR 0.40, 95% CI 0.19 to 0.83, p=0.01) but not hospitalisation up to 72 hours after discharge, compared with placebo.

- Pooled data from 3 RCTs (n=186) found intravenous ondansetron was more effective than placebo at stopping vomiting based on the proportion of children and young people who stopped vomiting (RR 2.01, 95% CI 1.49 to 2.71, p<0.00001, NNT 3 [95% CI 3 to 5]).

- In 3 of the 4 RCTs that compared oral ondansetron with placebo there was an increase in the number of episodes of diarrhoea (p<0.05). In 1 of the 3 RCTs that compared intravenous ondansetron with placebo, more episodes of diarrhoea were reported in the ondansetron group in the first 24 hours compared with placebo (p=0.013).

- The updated Cochrane review (Carter and Fedorowicz 2012) was well-conducted, but it is limited by the quality of the trials it included. The authors suggest that study design in the included studies was adequate overall but there was an unclear or high risk of bias in some of the domains, which reflects the challenges faced in screening and following up children and young people presenting to emergency departments.

- The 8 RCTs included in the updated Cochrane review that investigated ondansetron were conducted mostly in the emergency departments of children's hospitals in the USA, Canada, Turkey, Venezuela, Qatar and Thailand. The findings of these may not be generalisable to UK practice.

- The retrospective cohort study of ondansetron use in emergency departments of children's hospitals in the USA (Freedman et al. 2014) found oral ondansetron use increased from a median institutional rate of 0.11% of patient visits in 2002 to 42.2% in 2011. However, this increased use of oral ondansetron was not associated with reductions in the rates of intravenous rehydration (18.7% of children or young people during the low ondansetron use period and 17.8% during the high ondansetron use period) or hospitalisation (6.0% during the low ondansetron use period and 6.7% during the high ondansetron use period).

- This study is limited by its observational nature, and also reflects US not UK practice. However, it provides useful data to determine the clinical effectiveness of ondansetron in 'real-world' conditions.

- Ondansetron prolongs the QT interval in a dose-dependent manner and cases of Torsade de Pointes have been reported in people using ondansetron. Ondansetron should be avoided in people with congenital long QT syndrome and should be used with caution in people who have or may develop prolongation of QTc, such as people with electrolyte abnormalities, congestive heart failure, bradyarrhythmias or people taking other medicinal products that lead to QT prolongation or electrolyte abnormalities. Hypokalaemia and hypomagnesaemia should be corrected prior to ondansetron administration (see ondansetron summaries of product characteristics for details). Dose-dependent QT interval prolongation with ondansetron is discussed in more detail in the July 2013 Drug Safety Update from the MHRA.

Full text of Evidence review.

Context and estimated impact for the NHS

For the full NICE guideline on diarrhoea and vomiting caused by gastroenteritis in children younger than 5 years published in 2009, a simple economic model was developed. This showed potential economic advantages of oral ondansetron if given to children with persistent vomiting in whom intravenous fluids are being considered. However, there was clinical uncertainty about possible effects of ondansetron on diarrhoea, and whether or not increased diarrhoea would lead to increased use of NHS resources. Therefore no firm conclusions regarding the cost-effectiveness of ondansetron could be made.

- Ondansetron tablets are £1.71 for 10×4 mg tablets and £44.05 for 10×8 mg tablets (excluding VAT; Drug Tariff, September 2014).

- Ondansetron orodispersible tablets are £35.97 to £37.76 for 10×4 mg tablets and £71.94 to £75.53 for 10×8 mg tablets (excluding VAT; costs taken from the Drug Tariff, September 2014).

- Ondansetron 4 mg/5 ml oral solution is £36.82 for 50 ml (excluding VAT; costs taken from the Drug Tariff, September 2014).

- Ondansetron (Zofran) 2 mg/ml injection is £29.97 for 5×2 ml (4 mg) ampoules and £59.95 for 5×4 ml (8 mg) ampoules (excluding VAT; costs taken from MIMS September 2014).

Full text of Context and estimated impact for the NHS.

Information for the public

A plain English summary is available on the NICE website. This sets out the main points from the evidence summary in non-technical language and may be especially helpful for parents, carers or children with gastroenteritis who are being offered ondansetron to manage nausea and vomiting.

> **About this evidence summary**
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> 'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.
>
> The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.
>
> The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance**.

Full evidence summary

Introduction and current guidance

NICE published a clinical guideline on diarrhoea and vomiting caused by gastroenteritis: diagnosis, assessment and management in children younger than 5 years in 2009.

This guideline outlines that infective gastroenteritis in young children is characterised by the sudden onset of diarrhoea, with or without vomiting. The illness usually resolves without treatment within days; however, symptoms are unpleasant and affect both the child and family or carers. Severe diarrhoea can quickly cause dehydration, which may be life threatening. The guideline estimated that approximately 10% of children younger than 5 years present to healthcare services with gastroenteritis each year, and diarrhoeal illness accounted for 16% of medical presentations to a major paediatric emergency department in the UK.

The management of gastroenteritis in children is multifaceted, and the NICE guideline covers diagnosis, assessment of dehydration and shock, fluid management, nutritional management and the role of antibiotics and other therapies.

The full NICE guideline included a review of other interventions for gastroenteritis, including antiemetics, antidiarrhoeals, micronutrients and fibre, alternative and complementary therapies, and probiotics.

This stated that many children with gastroenteritis experience vomiting, particularly in the early phase of the illness, and this is a major factor leading to the failure of oral rehydration therapy. If vomiting could be treated effectively then there might be a reduction in the use of intravenous fluid therapy.

Various antiemetic agents have been used to prevent or reduce vomiting in children with gastroenteritis, including phenothiazines (such as prochlorperazine), antihistamines (such as cyclizine), metoclopramide, domperidone, ondansetron and dexamethasone. However, many of these are associated with safety concerns and none are licensed specifically for the management of nausea and vomiting in children with gastroenteritis.

The BNF for Children states that phenothiazines and metoclopramide can all induce acute dystonic reactions such as facial and skeletal muscle spasms and oculogyric crises, and

that children (especially girls, young women, and those under 10 kg) are particularly susceptible. See the BNF for Children section on drugs used in nausea and vertigo for more information.

Various safety concerns with antiemetics have been highlighted by the Medicines and Healthcare Products Regulatory Agency (MHRA). In the August 2013 issue of Drug Safety Update, the MHRA stated that the risk of neurological adverse effects with metoclopramide are higher in children than in adults; in the May 2014 issue of Drug Safety Update they highlighted the risks of cardiac side effects with domperidone, and in the July 2013 Drug Safety Update the dose-dependent QT interval prolongation with ondansetron was discussed.

The review of antiemetics in the full NICE guideline identified 5 relevant trials from a search to August 2008. These investigated oral ondansetron, intravenous ondansetron, intravenous metoclopramide and intravenous dexamethasone (see Evidence review section below for details).

After reviewing the evidence, the guideline development group stated, 'Although many children vomit during oral rehydration therapy, this is usually not so severe as to prevent oral rehydration. Occasionally, vomiting is frequent and persistent. In such cases, a decision might be made to administer oral rehydration salt solution by nasogastric tube or to change to intravenous fluid therapy. The availability of an effective antiemetic could therefore be very valuable. The guideline development group considered that evidence from randomised controlled trials (RCTs) indicated that oral ondansetron could increase the success rate with oral rehydration therapy. The guideline development group was concerned that ondansetron might have adverse effects such as worsening diarrhoea. There was no evidence to support other agents, including metoclopramide and dexamethasone. The guideline development group concluded that administration of antiemetics could not currently be recommended. However, the guideline development group did consider that further research on the use of ondansetron was needed, focusing particularly on the possible risk of worsened diarrhoea.'

Product overview

Drug action

Ondansetron is a potent, highly selective 5HT3 receptor antagonist. Its precise mode of

action in the control of nausea and vomiting is not known but it is probably due to antagonism of 5HT3 receptors on neurons located both in the peripheral and central nervous system (ondansetron summaries of product characteristics).

Regulatory status

Ondansetron is licensed for use in adults for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and the prevention and treatment of post-operative nausea and vomiting. In children and young people it is licensed for the management of chemotherapy-induced nausea and vomiting in children aged at least 6 months, and for the prevention and treatment of post-operative nausea and vomiting in children aged at least 1 month (see individual summaries of product characteristics for details).

Ondansetron is not licensed for the management of vomiting in children or young people with gastroenteritis, therefore using it for this indication is off-label.

In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using ondansetron outside its authorised indications.

Cost

Ondansetron is available as generic and branded products, and costs are as follows (excluding VAT; costs taken from the Drug Tariff, September 2014):

- ondansetron 4 mg tablets, £1.71 for 10 tablets

- ondansetron 4 mg oral lyophilisates sugar free, £35.97 for 10 tablets (Zofran Melt)

- ondansetron 4 mg orodispersible tablets, £37.76 for 10 tablets

- ondansetron 4 mg/5 ml oral solution sugar free, £36.82 for 50 ml

- ondansetron 8 mg tablets, £44.05 for 10 tablets

- ondansetron 8 mg oral lyophilisates sugar free, £71.94 for 10 tablets (Zofran Melt)

- ondansetron 8 mg orodispersible tablets, £75.53 for 10 tablets.

Zofran 2 mg/ml injection is £29.97 for 5×2 ml (4 mg) ampoules and £59.95 for 5×4 ml (8 mg) ampoules in MIMS September 2014 (excluding VAT).

Evidence review

This evidence summary is based on the evidence review of antiemetics for the full NICE guideline on diarrhoea and vomiting caused by gastroenteritis in children younger than 5 years published in 2009, an updated Cochrane review of antiemetics for acute gastritis in children and young people (Carter and Fedorowicz 2012) and a retrospective cohort study of ondansetron use in the emergency departments of children's hospitals in the USA (Freedman et al. 2014).

Clinical effectiveness

Evidence in the NICE clinical guideline

The review of antiemetics in the full NICE guideline identified 5 relevant trials from a search to August 2008 (n=639, children aged 6 months to 12 years). Four trials were from the USA and 1 was from Venezuela. Three RCTs investigated oral ondansetron compared with placebo (Ramsook et al. 2002, Freedman et al. 2006 and Roslund et al. 2008) and 2 investigated intravenous ondansetron compared with either intravenous dexamethasone and placebo (Stork et al. 2006) or intravenous metoclopramide and placebo (Cubeddu et al. 1997). All of these trials are included in the Cochrane review.

Cochrane review

A Cochrane review of antiemetics for reducing vomiting related to acute gastroenteritis in children and young people was published in 2011 (Fedorowicz et al. 2011). This included 7 RCTs (n=1020) in children and young people aged 5 months to 12 years, 4 of which investigated oral ondansetron compared with placebo (Ramsook et al. 2002, Freedman et al. 2006, Roslund et al. 2008 and Yilmaz et al. 2010). Two RCTs investigated intravenous ondansetron (Stork et al. 2006 and Cubeddu et al. 1997) and 1 investigated a dimenhydrinate suppository.

An update to this Cochrane review was published in BMJ Open in 2012 (Carter and Fedorowicz 2012). The update included 10 RCTs (n=1479); 7 from the original Cochrane review plus 2 further RCTs investigating intravenous ondansetron compared with either

intravenous metoclopramide (Al-Ansari et al. 2011) or placebo (Rerksuppaphol and Rerksuppaphol 2010), and 1 further RCT investigating oral granisetron. The 8 RCTs investigating ondansetron were conducted mostly in the emergency departments of children's hospitals in the USA, Canada, Turkey, Venezuela, Qatar and Thailand. Children and young people included in the trials were aged between 3 months and 13 years.

Dosing regimens varied between the studies but most used a weight-dependent dosage. Of the 4 RCTs investigating oral ondansetron, 2 used a single dose of an orodispersible tablet at a dose of 2 mg for children under 15 kg, 4 mg for children weighing between 15 and 30 kg and 6 or 8 mg for children over 30 kg. The other 2 RCTs used multiple 8-hourly doses of an ondansetron solution. In 1 study, 6 doses of 1.6 mg for children aged 6 months to 1 year, 3.2 mg for children aged 1 to 3 years and 4 mg for children aged 4 to 12 years were given. In the other study, 3 doses of 0.2 mg/kg were given. Of the 4 RCTs investigating intravenous ondansetron, 3 used a single dose of 0.15 mg/kg and 1 used a single dose of 0.3 mg/kg.

The primary outcome of the Cochrane review was the time taken from the first administration of the treatment until vomiting stopped, but none of the trials of oral ondansetron reported this. Pooled data from the 4 RCTs (n=574) which compared oral ondansetron with placebo (Ramsook et al. 2002, Freedman et al. 2006, Roslund et al. 2008 and Yilmaz et al. 2010) found ondansetron was more effective at stopping vomiting based on the proportion of children and young people who stopped vomiting (relative risk [RR] 1.44, 95% confidence interval [CI] 1.29 to 1.61, p<0.00001) with a number needed to treat (NNT) of 4 (95% CI 4 to 6). Substantial heterogeneity was noted and attributed to 1 study (Yilmaz et al. 2010), but when this was removed the result was similar (RR 1.33, 95% CI 1.19 to 1.49, p<0.00001, n=465).

Secondary outcomes included intravenous rehydration, hospitalisation and adverse events. In a pooled analysis of data from 3 of the RCTs (n=465) which compared oral ondansetron with placebo (Ramsook et al. 2002, Freedman et al. 2006 and Roslund et al. 2008), the proportion of children and young people needing intravenous fluid therapy was statistically significantly lower in the ondansetron group during the emergency department stay (RR 0.41, 95% CI 0.29 to 0.59, p<0.00001, NNT 5 [95% CI 4 to 8]) and up to 72 hours after discharge. Pooled data from these same studies found ondansetron reduced the immediate hospital admission rate during the emergency department stay (RR 0.40, 95% CI 0.19 to 0.83, p=0.01) but not hospitalisation up to 72 hours after discharge. There was no difference between oral ondansetron and placebo for emergency department revisit rates.

In the 3 RCTs which compared intravenous ondansetron with placebo, only 1 (Rerksuppaphol and Rerksuppaphol 2010, n=74) reported data for the primary outcome. This found that the time taken from the first administration of the treatment until cessation of vomiting was statistically significantly reduced with ondansetron (last vomiting after drug administration: mean 4.2±11.3 hours in the ondansetron group and 13.5±13.6 hours in the placebo group, p<0.01). Pooled data from the 3 RCTs (Cubeddu et al. 1997, Stork et al. 2006 and Rerksuppaphol and Rerksuppaphol 2010, total n=186) found intravenous ondansetron was more effective than placebo at stopping vomiting based on the proportion of children and young people who stopped vomiting (RR 2.01, 95% CI 1.49 to 2.71, p<0.00001, NNT 3 [95% CI 3 to 5]). However, there was heterogeneity between the studies, possibly because of their small sample size.

Two RCTs (Al-Ansari et al. 2011, n=186 and Cubeddu et al. 1997, n=36) compared intravenous ondansetron with intravenous metoclopramide (0.3 mg/kg). These trials found no statistically significant differences between the drugs in various outcomes. However, the updated Cochrane review authors stated that both RCTs were underpowered superiority studies and could only demonstrate no evidence of a difference between the drugs.

The authors of the updated Cochrane review (Carter and Fedorowicz 2012) carried out a mixed treatment comparison analysis using both direct and indirect evidence to estimate which was the most likely treatment to stop children and young people from vomiting. This has limitations, but found that oral or intravenous ondansetron was the treatment most likely to be effective compared with intravenous metoclopramide, oral granisetron, intravenous dexamethasone or placebo. No evidence on the use of cyclizine or domperidone was included in this systematic review.

Since this review was published, 2 further RCTs have been published comparing oral ondansetron with placebo in the emergency department of an Iranian children's hospital (Golshekan et al. 2013, n=176) and oral ondansetron with oral domperidone in the outpatient department of a hospital in Thailand (Rerksuppaphol and Rerksuppaphol 2013, n=76). These small studies have not been reviewed further in this evidence summary. There is also an Italian RCT (n=356) comparing oral ondansetron with oral domperidone and placebo which has been completed but not yet published (ClinicalTrials.gov Identifier: NCT01257672).

Observational study

In 2014, a retrospective cohort study of ondansetron use in the emergency departments of children's hospitals in the USA was published (Freedman et al. 2014). The objective of this study was to determine whether increasing emergency department use of oral ondansetron had resulted in a reduction in intravenous rehydration rates.

The cohort included 804,000 eligible patient visits across 18 children's hospital emergency departments in the USA between January 2002 and December 2011. Patients were children and young people aged less than 18 years who had a diagnosis of acute gastroenteritis (mean age 3.1 years [standard deviation 3.9 years]). Administration of oral ondansetron was identified for each patient through database review (no information on the dose or formulation of oral ondansetron administered was given). Visits were then categorised based on institutional use of ondansetron as low use (<5% of patients with acute gastritis received ondansetron), medium use (5 to 25% of patients with acute gastritis received ondansetron) or high use (more than 25% of patients with acute gastritis received ondansetron), and hospital-level analyses of the association between ondansetron use and various outcomes was conducted. The primary outcome was the proportion of children or young people given intravenous rehydration. Secondary outcomes included the proportion of children or young people who were hospitalised and the proportion who revisited the emergency department within 3 days.

Overall, oral ondansetron use increased from a median institutional rate of 0.11% (interquartile range 0.04% to 0.44%) of patient visits in 2002 to 42.2% (interquartile range 37.5% to 49.1%) in 2011 (p<0.001). However, this increased use of oral ondansetron was not associated with reductions in the rates of intravenous rehydration or hospitalisation. Intravenous rehydration was given to 18.7% of children or young people during the low ondansetron use period and 17.8% during the high ondansetron use period. The hospitalisation rate was 6.0% during the low ondansetron use period and 6.7% during the high ondansetron use period. Increased use of oral ondansetron was, however, associated with a decrease in emergency department revisits within 3 days from 5.7% during the low-use period to 5.0% during the high-use period (p<0.05).

Most children and young people receiving intravenous rehydration did not receive oral ondansetron and the authors suggest that although oral ondansetron use has increased, it may not be being targeted to those most likely to fail oral rehydration therapy (no information on the use of oral rehydration therapy was given). Alternatively, they suggest that intravenous rehydration may be being used excessively. Of the children and young people given intravenous rehydration, 13.5% were given oral ondansetron, but 54.1%

received intravenous ondansetron. The authors suggest that these patients may not be being given the opportunity to benefit from oral ondansetron in conjunction with oral rehydration therapy.

Safety and tolerability

During the review of antiemetics for the full NICE guideline on diarrhoea and vomiting caused by gastroenteritis in children younger than 5 years, the guideline development group expressed concern that ondansetron might have adverse effects such as worsening diarrhoea. They stated that if ondansetron does worsen diarrhoea it would be crucially important to determine the clinical significance of this effect, for example in relation to the risk of dehydration recurring or re-admission to hospital.

The updated Cochrane review (Carter and Fedorowicz 2012) found that in 3 of the 4 RCTs that compared oral ondansetron with placebo (Ramsook et al. 2002, Freedman et al. 2006 and Yilmaz et al. 2010), there was an increase in the number of episodes of diarrhoea (p<0.05). Other side effects included a single episode of macular rash in the ondansetron group and a single episode of urticaria with placebo. However, the authors point out the limitation that none of the studies were powered to detect rare but serious adverse effects.

In Ramsook et al. 2002, there was no statistically significant difference between groups in the numbers of episodes of diarrhoea while undergoing rehydration in the emergency department. However, over the next 48 hours, children receiving ondansetron had statistically significantly more diarrhoea than those receiving placebo. In the first 24-hour period, the mean number of diarrhoeal episodes in the ondansetron group (n=64) was 4.70 compared with 1.37 in the placebo group (n=54; p=0.002) and in the second 24 hours was 2.98 episodes (n=62) compared with 0.96 episodes (n=51; p=0.015).

In Freedman et al. 2006, the mean number of diarrhoeal episodes while undergoing rehydration was statistically significantly higher in children who had received ondansetron (mean 1.40, n=107) compared with the placebo group (mean 0.50, n=107; p<0.001) even after adjustment for number of episodes prior to admission.

In Yilmaz et al. 2010, at 8 hours there was no statistically significant difference in diarrhoeal episodes between the groups (mean 2.14 with ondansetron [n=55] compared with 2.0 with placebo [n=54]). However, children who received ondansetron had more episodes of diarrhoea while undergoing rehydration than those who received placebo at

24 hours (mean 5.04 with ondansetron [n=55] compared with 4.3 with placebo [n=54];
p=0.04).

In the 3 RCTs that compared intravenous ondansetron with placebo, 2 trials did not report
the presence of any significant side effects. In 1 RCT (Cubeddu et al. 1997), more episodes
of diarrhoea were reported in the ondansetron group in the first 24 hours compared with
placebo (p=0.013).

The authors of the updated Cochrane review concluded that there is an increased
incidence of diarrhoea when using ondansetron, but this is likely to vary according to the
dosage. It may also be that the increase in diarrhoea is the result of retention of fluids
which would otherwise been removed by vomiting.

The retrospective cohort study of ondansetron use in the emergency departments of
18 children's hospitals in the USA (Freedman et al. 2014) provided no information on safety
or tolerability.

The summaries of product characteristics for ondansetron state that hypersensitivity
reactions have been reported in people who have exhibited hypersensitivity to other
selective 5HT3 receptor antagonists. Respiratory events should be treated
symptomatically and clinicians should pay particular attention to them as precursors of
hypersensitivity reactions.

Ondansetron prolongs the QT interval in a dose-dependent manner and cases of Torsade
de Pointes have been reported in people using ondansetron. Ondansetron should be
avoided in people with congenital long QT syndrome and should be used with caution in
people who have or may develop prolongation of QTc, such as people with electrolyte
abnormalities, congestive heart failure, bradyarrhythmias or people taking other medicinal
products that lead to QT prolongation or electrolyte abnormalities. Hypokalaemia and
hypomagnesaemia should be corrected prior to ondansetron administration (see
ondansetron summaries of product characteristics for details). Dose-dependent QT
interval prolongation with ondansetron is discussed in more detail in the July 2013 Drug
Safety Update from the MHRA.

The summaries of product characteristics also state that there have been reports of
people experiencing serotonin syndrome (including altered mental status, autonomic
instability and neuromuscular abnormalities) following the concomitant use of ondansetron
and other serotonergic drugs, such as selective serotonin reuptake inhibitors (SSRIs) and

serotonin noradrenaline reuptake inhibitors (SNRIs). Ondansetron is known to increase large bowel transit time and people with signs of subacute intestinal obstruction should be monitored following administration.

Very common or common side effects (reported in at least 1 in 100 people) listed in the summaries of product characteristics for ondansetron are headache, a sensation of warmth or flushing and constipation. Uncommon side effects (reported in between 1 in 100 and 1 in 1000 people) are hiccups, seizures, movement disorders (including extrapyramidal reactions), arrhythmias, chest pain with or without ST segment depression, bradycardia, hypotension and asymptomatic increases in liver function tests.

Evidence strengths and limitations

The updated Cochrane review (Carter and Fedorowicz 2012) included 10 RCTs (n=1479). Whilst the review was well-conducted, it is limited by the quality of the trials it included. The authors suggest that study design in the included studies was adequate overall but there was an unclear or high risk of bias in some of the domains (for example random sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting). They suggest this reflects the challenges faced in screening and following up children and young people presenting to emergency departments.

The outcomes reported in the included studies were generally clinician centred outcomes rather than patient or parent preferred outcomes. For example, none of the RCTs of oral or intravenous ondansetron reported parenteral satisfaction and only 1 RCT of intravenous ondansetron reported the time taken from the first administration of the treatment until vomiting stopped.

The 8 RCTs included in the updated Cochrane review that investigated ondansetron were conducted in the emergency departments of children's hospitals in the USA, Canada, Turkey, Venezuela, Qatar and Thailand. The findings of these may not be generalisable to UK practice. It is also difficult to define a usual dose of oral or intravenous ondansetron for the management of nausea and vomiting in children and young people with gastroenteritis because the doses used in the studies were weight dependent and the dose, dosing schedule and formulation varied considerably between the studies.

The authors of the updated Cochrane review (Carter and Fedorowicz 2012) carried out a mixed treatment comparison analysis using both direct and indirect evidence. Although these analyses are useful to assess treatments that have not been compared in direct

head-to-head clinical trials, they have limitations and are no substitute for large, well-designed RCTs. They are based on many assumptions and are only as good as the data that are included.

The retrospective cohort study of ondansetron use (Freedman et al. 2014) is limited by its observational nature; in that bias and confounding is an issue. The authors did adjust the findings for age, sex, race, season, admission time and prior visit for acute gastroenteritis, laboratory testing, diagnostic imaging and rotavirus diagnosis; however some residual confounding may remain. The authors state that misclassification of patient visits is also a possibility and the increasing use of diagnostic testing and treatments in emergency departments over time may have affected the findings. The results of this study may not be generalisable to non-children's hospital settings or to UK practice, because the study was conducted in the emergency departments of children's hospitals in the USA. However, it provides useful data to determine the clinical effectiveness of ondansetron in 'real-world' conditions.

Context and estimated impact for the NHS

Cost effectiveness

For the full NICE guideline on diarrhoea and vomiting caused by gastroenteritis in children younger than 5 years published in 2009, a simple economic model was developed. This showed potential economic advantages of oral ondansetron if given to children with persistent vomiting in whom intravenous fluids are being considered. The guideline development group concluded that the use of ondansetron may be effective in stopping vomiting and may in turn help with the successful delivery of oral rehydration therapy, thereby reducing the need to treat with intravenous fluid therapy. This would have cost-saving implications for the NHS through fewer admissions for intravenous fluid therapy. However, there was clinical uncertainty about possible effects of ondansetron on diarrhoea, and whether or not increased diarrhoea would lead to increased use of NHS resources. Therefore no firm conclusions regarding the cost-effectiveness of ondansetron could be made.

An economic analysis of oral ondansetron use for children with gastroenteritis in US and Canadian emergency departments has been published (Freedman et al. 2010), but this may not be applicable to UK practice.

Current drug usage

No estimate of the current use of off-label ondansetron for the management of nausea and vomiting in children with gastroenteritis in UK clinical practice was identified.

Information for the public

A plain English summary is available on the NICE website. This sets out the main points from the evidence summary in non-technical language and may be especially helpful for parents, carers or children with gastroenteritis who are being offered ondansetron to manage nausea and vomiting.

Relevance to NICE guidance programmes

This use of ondansetron is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

NICE has issued a clinical guideline on diarrhoea and vomiting caused by gastroenteritis: diagnosis, assessment and management in children younger than 5 years. See introduction and current guidance section.

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Development of this evidence summary

The integrated process statement sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

No relevant interests declared.

About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance**.

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