

Promoting tolerance of enteral feeds in children and young people: domperidone

Evidence summary

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www.nice.org.uk/guidance/esuom18

Key points from the evidence

The content of this evidence summary was up-to-date in July 2013. 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

Only 1 small (n=22) partially blinded, randomised [crossover](#) study was identified. It found domperidone had a [statistically significant](#) benefit in the short term for improving gastric emptying times in very low birth weight preterm neonates receiving enteral feeds. No relevant studies were found in children and young people. This study provides only very limited evidence on the effectiveness, safety and tolerability of domperidone when used for promoting tolerance of enteral feeds in either the short or longer term.

Regulatory status: Off-label.

Effectiveness <ul style="list-style-type: none">• One small study (n=22) reporting on gastric emptying times as a primary outcome:<ul style="list-style-type: none">– domperidone had a statistically significant benefit when compared with a control (sterile water) on gastric emptying times and stool frequency over a 48-hour period– clinical or patient outcomes, such as effect on tolerance of enteral feeds, survival or nutritional status, were not evaluated.	Safety <ul style="list-style-type: none">• Domperidone has been associated with adverse cardiac effects, including QT prolongation and arrhythmias.• The European Medicines Agency is currently reviewing the benefit–risk balance of domperidone-containing medicines.
Patient factors <ul style="list-style-type: none">• Assessment of tolerability is difficult from the study assessed as only 22 neonates were included.• Summary of Product Characteristics recommends that the dose (for its licensed indications) should be determined accurately and followed strictly in neonates, infants, toddlers and small children.	Resource implications <ul style="list-style-type: none">• Domperidone is available in various formulations with costs ranging from £1.14 for a 30-pack of 10 mg tablets to £12.53 for 200 ml of 1 mg/ml oral suspension.

Key points

Domperidone 1 mg/ml oral suspension, 30 mg suppositories and some brands of 10 mg tablets are licensed for relieving symptoms of nausea and vomiting in children. None of the formulations are licensed for stimulating gastrointestinal motility to promote tolerance of enteral feeds in any age group, so use for this indication is off-label.

- There is very limited published evidence on using domperidone in children and young

people for this specific off-label indication. Just 1 relevant study, a small (n=22) partially blinded, randomised crossover study, was found that included an enterally fed neonatal population ([Gounaris et al. 2010](#)). No further studies were found that used domperidone to stimulate gastrointestinal motility to promote tolerance of enteral feeds in children and young people.

The study investigated using domperidone oral solution to improve gastric emptying in enterally fed very low birth weight preterm neonates in an intensive care setting.

All neonates received 200 ml/kg/day of milk by nasogastric tube and were also randomised to receive either domperidone oral solution (0.3 mg/kg/8 hours) or a control treatment (an equivalent quantity of sterile water) for a 48-hour treatment period.

The study found that neonates had shorter mean gastric emptying times when receiving domperidone (47.6 minutes, standard deviation [SD] 23.9 minutes) compared with sterile water (68.2 minutes, SD 25.5 minutes) and this difference was statistically significant ($p=0.008$). Stool frequency was also statistically significantly increased using domperidone compared with water (mean number of stools passed in 48 hours: 2.4 compared with 1.8, $p=0.038$). Frequency of vomiting was reported as being similar in both groups.

The clinical and patient impact of these gastric motility improvements in terms of improving enteral feeding tolerance and the ability to maintain adequate nutrition was not directly measured and so is unclear.

The reliability and generalisability of the evidence from this single study is very limited because of its small sample size, short treatment duration and narrowly defined neonate population. The results are not generalisable to non-neonate populations including older children and young people.

The study was too small and short term to assess side effects or safety reliably.

The summaries of product characteristics for licensed domperidone products carry the precaution that the drug may be associated with an increased risk of serious ventricular arrhythmias (very rare, frequency of less than 1 in 10,000), QT_c interval prolongation (an alteration of the electrical activity in the heart; frequency unknown) or sudden cardiac death (frequency unknown). Domperidone should therefore be used with caution in people who have existing prolongation of cardiac conduction intervals, particularly QT_c, and in people with significant electrolyte disturbances or underlying cardiac diseases such as

congestive heart failure. Use of the lowest effective dose of domperidone is recommended in adults and children and use in combination with potent CYP3A4 inhibitors that prolong the QT_c interval (for example, ketoconazole or erythromycin) should be avoided.

On 7 March 2013, the [European Medicines Agency](#) started a [safety review of domperidone-containing medicines](#) in relation to continued concerns about its adverse effects on the heart. No expected date for the final decision has been given.

Update

The following information has become available since this ESUOM was produced:

January 2015: NICE guideline on gastro-oesophageal reflux disease: recognition, diagnosis and management in children and young people published.

This guidance was mentioned in this evidence summary when it was first published as being in development. The NICE guideline on [gastro-oesophageal reflux disease: recognition, diagnosis and management in children and young people](#) has now been published. It recommends that healthcare professionals should not offer metoclopramide, domperidone or erythromycin to treat gastro-oesophageal reflux or gastro-oesophageal reflux disease without seeking specialist advice and taking into account their potential to cause adverse events. See the NICE guideline for more information.

30 September 2014: Domperidone: risks of cardiac side effects - indication restricted to nausea and vomiting, new contraindications, and reduced dose and duration of use.

A European review has confirmed that domperidone is associated with a small increased risk of serious cardiac side effects. Its use is now restricted to the relief of nausea and vomiting and the dosage and duration of use have been reduced. It should no longer be used for the treatment of bloating and heartburn. Domperidone is now contraindicated in those with underlying cardiac conditions and other risk factors. See the Medicines and Healthcare Products Regulatory Agency [Drug Safety Update May 2014](#) for more information.

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.**

Overview for healthcare professionals

Domperidone is a dopamine receptor antagonist that is used to relieve symptoms of nausea and vomiting in adults and children. It is also used to relieve symptoms of indigestion or feelings of discomfort or fullness in the stomach in adults.

Regulatory status of domperidone

Domperidone 10 mg tablets, 1 mg/ml oral suspension and 30 mg suppositories are licensed in the UK for relieving symptoms of nausea and vomiting, epigastric sense of fullness, upper abdominal discomfort and regurgitation of gastric contents in adults. In children, domperidone 1 mg/ml oral suspension, 30 mg suppositories and some brands of 10 mg tablets are licensed for relieving symptoms of nausea and vomiting. None of the formulations (tablets, oral suspension or suppositories) are licensed for stimulating gastrointestinal motility to promote tolerance of enteral feeds in any age group, so use for this indication is off-label. The oral suspension is the most likely formulation to be used off-label for this indication in infants because of its acceptability to infants and because it allows the smaller doses that are likely to be needed in younger children to be administered more accurately.

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 domperidone outside its authorised indications.

Evidence statements

- One small (n=22) and short-term, partially blinded, randomised crossover study ([Gounaris et al. 2010](#)) found that giving domperidone oral solution 0.3 mg/kg/8 hours over 48 hours led to a statistically significant improvement in gastric emptying time compared with a control (sterile water) in preterm, very low birth weight neonates being enterally fed in an intensive care unit.
- The number of stools passed also statistically significantly increased when using domperidone compared with water, but frequency of vomiting was described as similar in both groups.
- The clinical and patient impact of these findings in terms of improving enteral feeding tolerance and the ability to maintain adequate nutrition was not directly measured and so is unclear.
- The small sample size, narrow study population and short treatment duration in this study severely limit its ability to reliably assess whether domperidone is effective at promoting tolerance of enteral feeds in the study population as well as in wider populations of children and young people, or for longer periods of time.
- Although the authors report that no side effects were experienced by neonates in the study, reliable evidence of the safety of domperidone cannot be established because of the short-term nature of the treatment period.
- No further studies were found that used domperidone to stimulate gastrointestinal motility to promote tolerance of enteral feeds in children and young people.
- On 7 March 2013, the [European Medicines Agency](#) started a new [safety review of domperidone-containing medicines](#) in relation to continued concerns about its adverse effects on the heart. No expected date for the final decision has been given.

Summary of the evidence

This section gives a brief summary of the main evidence. A more thorough analysis is given in the [Evidence review](#) section.

Domperidone 10 mg tablets, 1 mg/ml oral suspension and 30 mg suppositories are licensed in the UK for the relief of symptoms of nausea and vomiting, epigastric sense of fullness, upper abdominal discomfort and regurgitation of gastric contents in adults. In children

domperidone 1 mg/ml oral suspension, 30 mg suppositories and some brands of 10 mg tablets are licensed for the relief of symptoms of nausea and vomiting. There are currently no UK treatments licensed for children and young people (under 18) to promote tolerance of enteral feeds. Consequently, using domperidone to promote tolerance of enteral feeds in this group represents off-label use.

Efficacy

There was very limited directly applicable research relevant to this specific off-label use of domperidone. For important evidence selection information, see the [Evidence selection](#) section.

The only relevant published information found came from a single non-UK-based study ([Gounaris et al. 2010](#)). This was a small (n=22), randomised, crossover study involving enterally fed very low birth weight preterm neonates with a clinical history of problems with gut motility in an intensive care setting. The authors describe the study as partially blinded, but it is not clear who was blind to treatments other than the radiologists involved in taking measurements of gastric emptying times in the neonates.

The study was small and short term, so cannot provide reliable or generalisable information on the effectiveness or safety of domperidone in children and young people for this off-label use.

In the single study identified ([Gounaris et al. 2010](#)), all very low birth weight preterm neonates were given 200 ml/kg/day of milk (either standard premature infant formula [n=12] or their mother's own supplemented milk [n=10]) by nasogastric tube. In addition, they received either domperidone oral solution (0.3 mg/kg/8 hours) or a control treatment (an equivalent quantity of sterile water) for a 48-hour treatment period. The primary outcome was change in gastric emptying time. Secondary outcomes included the number of stool passages in both groups and the differences in gastric emptying between neonates fed with formula milk and those fed with their mother's own supplemented milk.

The study found that neonates had shorter mean gastric emptying times when receiving domperidone (47.6 minutes, [standard deviation](#) [SD] 23.9 minutes) compared with sterile water (68.2 minutes, SD 25.5 minutes) and this difference was [statistically significant](#) ($p=0.008$). Stool frequency was also statistically significantly increased using domperidone compared with water (mean number of stools passed in 48 hours: 2.4 compared with 1.8, $p=0.038$). Frequency of vomiting was reported as being similar in both

groups. No further clinical or patient outcomes of feeding tolerance were recorded, such as nutrient absorption, or the impact on growth or survival.

The reliability and generalisability of the evidence from this single study is very limited because of its small sample size, short treatment duration and narrowly defined neonate population. The results are not generalisable to non-neonate populations including older children and young people.

The typical cost of using off-label domperidone to promote tolerance of enteral feeds and to stimulate gut motility could not be established because of lack of information on typical off-label dosing and treatment duration.

Table 1 Summary of the crossover study: Gounaris et al. (2010)

	Domperidone (0.3 mg/kg/ 8 hours over 48 hours)	Sterile water (same quantity as domperidone over 48 hours)	Analysis
Randomised ^a	n=22	n=22	All 22 participants completed the trial and were included in the analysis
Efficacy			
Primary outcome: gastric emptying, ultrasound measurement of ACSA (mean half-value time, minutes)	47.6 (SD 23.9)	68.2 (SD 25.5)	p=0.008 Absolute difference=20.6 minutes after the 48-hour treatment period
Secondary outcome: mean number of stools passed during 48-hour treatment period	2.4 (SD 1.9)	1.8 (SD 0.7)	p=0.038 Absolute difference=0.6 stools during the 48-hour treatment period
Other outcomes:			

Number of times vomiting occurred	Not reported	Not reported	The publication reported no difference between groups in the number of times vomiting occurred
Gastric residual	Not reported	Not reported	
Abdominal distension	Not reported	Not reported	
Safety			
Adverse events	Not reported	Not reported	The publication reported there were 'no adverse effects'
<p>Abbreviations: ACSA, antral cross-sectional area; n, number of patients; SD, standard deviation.</p> <p>^a The study was a crossover design, so all neonates received both treatments with treatment order determined by randomisation. All neonates were on full enteral feeding during study treatment and received 200 ml/kg/day of milk by nasogastric tube given by gravity.</p>			

Safety

The study was too small and too short for side-effect frequencies or safety to be assessed reliably.

The [summaries of product characteristics](#) for licensed domperidone products contain the precaution that epidemiological studies have shown that domperidone may be associated with an increased risk of serious ventricular arrhythmias (very rare, frequency of less than 1 in 10,000), QT_c interval prolongation (an alteration of the electrical activity in the heart; frequency unknown) or sudden cardiac death (frequency unknown). They specify that domperidone should be used with caution in people who have existing prolongation of cardiac conduction intervals, particularly QT_c, and in people with significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure. They also recommend that domperidone should be used at the lowest effective dose in adults and children and that using it in combination with potent CYP3A4 inhibitors that prolong the QT_c interval should be avoided.

On 7 March 2013, the [European Medicines Agency](#) started a [safety review of](#)

domperidone-containing medicines in relation to continued concerns about its adverse effects on the heart. The European Medicines Agency will review all available data on the benefit–risk balance of domperidone-containing medicines, and issue an opinion on whether their marketing authorisations should be maintained, varied, suspended or withdrawn across the European Union. No expected date for the final decision has been given.

Cost effectiveness and cost

No information on the typical dose or treatment duration of off-label domperidone to promote tolerance of enteral feeds in children and young people was available at the time this evidence summary was prepared. Therefore, it was not possible to estimate daily, weekly or monthly costs with any degree of certainty.

The NHS Electronic Drug Tariff (July 2013) lists the price for domperidone formulations as follows:

- Domperidone 10 mg tablet, 30-tablet pack: £1.14
- Domperidone 10 mg tablet, 100-tablet pack: £3.80
- Domperidone 30 mg suppositories, 10-suppository pack: £3.06
- Domperidone 1 mg/ml oral suspension sugar free, 200 ml pack: £12.53

Relevance to NICE guidance programmes

The off-label use of domperidone is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

Domperidone is mentioned very briefly in 2 NICE clinical guidelines, neither specifically relating to its use in promoting tolerance of enteral feeds in children and young people:

- Dyspepsia: management of dyspepsia in adults in primary care (NICE clinical guideline 17) states evidence is sparse about using domperidone as a prokinetic in the treatment of dyspepsia.
- Type 2 diabetes – newer agents (partial update of CG66) (NICE clinical guideline 87) says to consider a trial of metoclopramide, domperidone or erythromycin for an adult

with gastroparesis. This is in relation to the secondary effects of type 2 diabetes.

A NICE clinical guideline on gastro-oesophageal reflux in children and young people is in development. It is expected to be published in October 2014 and will include the effectiveness of prokinetic agents for gastro-oesophageal reflux.

Intervention and alternatives

The [British national formulary](#) describes domperidone as a dopamine receptor antagonist that stimulates gastric emptying and small intestinal transit, and enhances the strength of oesophageal sphincter contractions.

There are currently no treatments licensed in the UK for promoting tolerance of enteral feeds in children and young people.

Condition

Enteral feeding, also known as tube feeding, is a way of providing adequate nutrition to a person who is undernourished or at risk of becoming so. In premature babies this can be because their suck and swallow coordination has not developed fully, meaning they can't get enough milk to grow and develop adequately (failure to thrive). In older children or young people, enteral feeding may be needed if they are unconscious in a hospital intensive care unit.

Enteral feeding involves delivering nutrition down a tube that has been passed into the stomach, duodenum or jejunum through the nose (nasogastric, nasojejunal or nasoduodenal tubes), the mouth (orogastric tube), or directly through the abdomen (percutaneous endoscopic gastrostomy [PEG] or percutaneous jejunostomy feeding tubes). Nasogastric tubes are the most commonly used type of feeding tube.

The normal movement and absorption of food as it travels through the stomach and digestive system is coordinated by hormones released during chewing. These and related cues signal the stomach to empty into the intestine in the presence of nutrients. Because enteral feeding bypasses the need to chew, this process is sometimes disrupted, causing food to sit in the stomach for too long without it moving into the intestines to be absorbed (delayed gastric emptying). This can cause gastrointestinal symptoms such as abdominal bloating, cramps, nausea, diarrhoea and constipation. These symptoms are often broadly

described as feeding intolerance.

Enteral feeding intolerance is a common problem in preterm infants in intensive care ([Ng and Shah 2008](#)). This is because many aspects of the gastrointestinal motility systems of neonates are immature, causing further delays in the transit of food through the digestive system, in addition to those associated with enteral feeding. Feeding intolerance can affect a preterm infant's ability to maintain adequate nutrition, and can potentially affect survival ([Gounaris et al. 2010](#)).

Feeding intolerance in preterm neonates can present as regurgitation, vomiting, abdominal swelling and delayed passing of stools. Residual food is sometimes noted in the stomach before the next scheduled feeding time ([Ng and Shah 2008](#) and [Gounaris et al. 2010](#)).

Alternative treatment options

No licensed treatments are currently available in the UK for stimulating gastrointestinal motility in children and young people being enterally fed to promote tolerance of enteral feeds.

The [British national formulary for children](#) states that a low dose of erythromycin stimulates gastrointestinal motility and may be used on the advice of a paediatric gastroenterologist to promote tolerance of enteral feeds, but that erythromycin may be less effective as a prokinetic drug in preterm neonates than in older children. It should be noted that erythromycin is not licensed for promoting tolerance of enteral feeds and this represents off-label use.

Alternative pharmacological treatment options for improving gut motility described in the study by [Gounaris et al. \(2010\)](#) include metoclopramide (off-label), bethanechol (off-label), erythromycin (off-label) and cisapride ([withdrawn from marketing in the UK in 2000](#) because of safety concerns).

Evidence review: efficacy

During the development of this evidence summary, a search was carried out for published studies using domperidone to promote tolerance of enteral feeds in children and young people (under the age of 18). No publication date or study design search limitations were used in the initial search. For important evidence selection information, see the [Evidence](#)

selection section.

The search highlighted a very limited amount of directly applicable research relevant to this specific off-label use of domperidone. The most relevant published information came from a single study ([Gounaris et al. 2010](#)), which was a small randomised, crossover study in very low birth weight preterm neonates receiving enteral feeding. The authors describe the study as partially blinded, but it is not clear who was blind to treatments other than the radiologists involved in measuring gastric emptying times in the neonates.

Because of the small sample size (n=22) and short-term nature (48-hour treatment) of the study, its results have limited reliability for determining the effectiveness of domperidone in these neonates. Its results also have limited applicability to the use of domperidone for promoting the tolerance of enteral feeds in older children and young people.

The study, based in Greece, included 22 preterm (gestational age less than 34 weeks, mean age 30.2 weeks) very low birth weight neonates (birth weight less than 2000 grams, mean weight 1377 grams) with a clinical history of 1 or more problems in gut motility, such as regurgitation, vomiting, abdominal distension and delay in stool passage.

All neonates were fully enterally fed, receiving 200 ml/kg/day of milk (either standard premature infant formula [n=12] or their mother's own supplemented milk [n=10]) by nasogastric tube given by gravity. In addition, neonates were randomised to first receive either domperidone (Cilroton, Janssen) at a dose of 0.3 mg/kg/8 hours or an equal quantity of sterile water (the control group), given for a 48-hour period. This was followed by a 1 to 3-day treatment-free washout period. Then a second 48-hour treatment period was started in which the neonates were switched to the other treatment option (a crossover design).

Gastric emptying was the primary outcome and the authors report that this was measured on 2 occasions in each infant; first on administration of domperidone and second after discontinuation of domperidone while receiving an equal quantity of sterile water for an additional 48-hour period. The authors state that 11 infants received domperidone before the first measurement of gastric emptying and the other 11 infants received domperidone after sterile water treatment just before the second measurement. Gastric emptying was assessed by ultrasound using serial measurements of the antral cross-sectional area (ACSA) of the stomach taken before enteral feeding, immediately after feeding, then every 10 minutes for the first half hour, and then every 30 minutes up to 2 hours. Two radiologists carried out the ultrasound assessments; both were blinded to the treatment

allocation of the neonates. The primary outcome and main statistical comparison was the average time (mean time, in minutes) it took the ACSA to reach half of its initial value after feeding in both groups, called the ACSA half-time.

Secondary outcomes included number of stools passed in the 48-hour treatment period and the differences in gastric emptying in neonates fed their mother's own supplemented milk compared with neonates fed formula milk. Throughout the study neonates were observed for gastric residual volume (considered significant if it exceeded 25% of the previous 2 hours' feeding volume), vomiting and abdominal distension. These were assessed and recorded by a nurse. All neonates completed the study and were included in the analysis.

The study found that neonates had shorter mean gastric emptying times (ACSA half-time) when receiving domperidone (47.6 minutes, standard deviation [SD] 23.9 minutes) compared with sterile water (68.2 minutes, SD 25.5 minutes). This was a statistically significant difference ($p=0.008$). In total, 18 of 22 neonates showed shorter gastric emptying times while on domperidone compared with water. In the other 4 neonates, 2 had a shorter gastric emptying time while receiving water and 2 showed equal times on both treatments.

For the secondary outcomes, the mean number of stools passed while receiving domperidone (2.4, SD 1.9) was statistically significantly greater than while receiving water (1.8, SD 0.7, $p=0.038$). There was no significant difference in gastric emptying between neonates receiving milk formula and those receiving their mother's supplemented milk ($p=0.418$ domperidone group, $p=0.610$ water group).

There were no differences between the 2 groups in the number of times vomiting occurred, but no figures were reported for this outcome. Similarly, no results were presented for gastric residual volume or frequency of abdominal distension.

Evidence review: safety

The randomised crossover study by Gounaris et al. (2010) reported there were no side effects in the 22 neonates treated. However, the study was too small ($n=22$) and short term (48-hour treatment) to provide reliable information on safety or side effects.

The contraindications in the summary of product characteristics (SPC) for licensed 1 mg/ml domperidone oral suspension (the formulation most likely to be used off-label to

promote tolerance of enteral feeds in children) indicate it should not be used when stimulation of gastric motility could be harmful, such as in people with gastrointestinal haemorrhage, mechanical obstruction or perforation. It is also contraindicated when there is a known hypersensitivity to domperidone or any of the excipients, and in the presence of a prolactin-releasing pituitary tumour (prolactinoma).

Precautions of using domperidone oral suspension in infants in the [SPC](#) include rare neurological side effects. It reports that since metabolic functions and the blood–brain barrier are not fully developed in the first months of life the risk of neurological side effects is higher in young children. Therefore, it recommends that the dose (for its licensed indications) be determined accurately and followed strictly in neonates, infants, toddlers and small children. The SPC also notes that overdosing may cause extrapyramidal symptoms in children.

The [British national formulary for children](#) states that prolactinaemia is a contraindication for use in children and that one of the rare side effects of domperidone may include hyperprolactinaemia.

The SPC also states in the [precautions for use and undesirable effects](#) sections that some epidemiological studies showed that domperidone may be associated with an increased risk of serious ventricular arrhythmias (very rare, frequency of less than 1 in 10,000), QT_c interval prolongation (an alteration of the electrical activity in the heart; frequency unknown) or sudden cardiac death (frequency unknown). It states that domperidone should be used at the lowest effective dose in adults and children.

Caution needs to be exercised when using domperidone and other drugs that prolong QT_c intervals in people who have existing prolongation of cardiac conduction intervals, particularly QT_c, and in people with significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure.

The main metabolic pathway of domperidone is through the enzyme CYP3A4 and therefore co-administration with oral ketoconazole, erythromycin or other potent CYP3A4 inhibitors that prolong the QT_c interval should be avoided.

In 2011, the [European Medicines Agency](#) Pharmacovigilance Working Party evaluated concerns about domperidone-related adverse heart effects, including QT_c interval prolongation and arrhythmias (unstable heartbeats). They recommended that all product information for domperidone be updated to reflect the risk of these cardiac adverse events

and that domperidone should be used with caution in people with certain heart conditions, including heart failure, a previous heart attack, angina (chest pains) and heart rhythm disorders.

In May 2012, the Medicines and Healthcare products Regulatory Agency issued a drug safety update, Domperidone: small risk of serious ventricular arrhythmia and sudden cardiac death. This stated that some epidemiological studies have shown that domperidone may be associated with a small increased risk of serious ventricular arrhythmia or sudden cardiac death. These risks may be higher in people older than 60 years and in people who receive daily oral doses of more than 30 mg. Non-prescription domperidone products are not recommended for use in people with underlying cardiac disease without medical supervision.

On 7 March 2013, the European Medicines Agency started a new safety review of domperidone-containing medicines in relation to continued concerns about its adverse effects on the heart. The European Medicines Agency will review all available data on the benefit–risk balance of domperidone-containing medicines, and issue an opinion on whether their marketing authorisations should be maintained, varied, suspended or withdrawn across the European Union. No expected date for the final decision has been given.

The European Medicines Agency advises that while the safety review is ongoing people should speak to their doctor or pharmacist if they have any questions or concerns.

Evidence review: economic issues

Cost

The unit costs of the different domperidone formulations are summarised below. The formulation of domperidone most likely to be used off-label for promoting tolerance of enteral feeds in children and young people is the oral suspension because of its acceptability in this group. It also allows more accurate administration of the smaller doses likely to be needed in younger children.

Formulation	Volume	Cost
Domperidone 10 mg tablets	30 tablets	£1.14

	100 tablets	£3.80
Domperidone 30 mg suppositories	10 suppositories	£3.06
Domperidone 1 mg/ml oral suspension sugar free	200 ml	£12.53
Source: NHS Electronic Drug Tariff (July 2013)		

No information on the typical dose or treatment duration of off-label domperidone to promote tolerance of enteral feeds in children and young people was available at the time this evidence summary was prepared. Therefore, it was not possible to estimate daily, weekly or monthly costs with any degree of certainty.

Current drug usage

[Prescription cost analysis for England 2012](#) shows that approximately 1,618,400 prescriptions for domperidone 10 mg tablets (branded and generic formulations) were dispensed at a cost of around £4,197,900, approximately 4000 prescriptions for Motilium Instants 10 mg orodispersible tablets were dispensed at a cost of around £65,500 and approximately 161,600 prescriptions for domperidone suspension 1 mg/ml (branded and generic formulations) at a cost of around £3,987,600. It is not known for which indications these were prescribed.

Evidence strengths and limitations

Overall, there was very limited published evidence showing whether using domperidone off-label improves tolerance of enteral feeds through stimulating gastrointestinal motility in children and young people being enterally fed.

The single relevant study focused on a very specific patient group – very low birth weight, preterm neonates in intensive care – so its results are not likely to be applicable to children or young people of other ages or in other care settings. In addition, some of the reporting of the study was unclear, for example, when measurements of gastric emptying time were taken. The authors report that randomisation was performed by a person not involved in the care of the neonates using sealed envelopes but it did not say if the envelopes were opaque therefore it was unclear whether allocation to treatment was concealed.

The study was small (n=22), meaning its results may not be reliable and may differ from

those in larger studies with more diverse populations. The treatment period used (48 hours) was short, meaning the study was unable to assess whether the effects of domperidone were temporary or whether they would be maintained over time. More importantly, the study was not large enough or long enough to give reliable safety information for short- or long-term off-label use of domperidone.

The strongest evidence on the safety of domperidone comes from the safety information contained in the summary of product characteristics of existing licensed domperidone formulations, supplemented by specific safety warnings and safety reviews by the Medicines and Healthcare products Regulatory Agency and European Medicines Agency respectively.

The study focused mainly on short-term gastric emptying and described (without providing figures) that vomiting did not differ between the 2 groups. It did not assess and report other patient-related outcomes of feeding tolerance, such as regurgitation, or clinically relevant outcomes such as nutrition absorption, growth or survival.

Summary for patients

A [summary written for patients](#) is available on the NICE website.

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Zentiva (2012) [Motilium 30 mg suppositories](#) [online; accessed 23 May 2013]

Development of this evidence summary

This evidence summary was developed for NICE by Bazian Ltd. 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.

Project team

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Declarations of interest

No relevant interests declared.

Appendix: Search strategy and evidence selection

Search strategy

General background, guidelines and technology assessments:

1. [NICE Evidence](#)
2. [NICE](#)
3. [Euroscan](#)
4. Broad internet search: [Google](#) e.g.: allintext: stasis or transit or motility or dysmotility or prokinetic or emptying domperidone OR motilium "children" filetype:pdf
5. [Scirus](#)

MEDLINE & Embase (via Ovid)

1. Domperidone/ (1500)
2. (domperidon\$ or gastrocure or r33812 or peridys or nauzelin or domidon or motilium).tw. (1920)
3. or 2 (2216)
4. exp INFANT/ (898300)
5. infant?.tw. (264474)
6. (newborn\$ or neonate\$).tw. (169408)
7. (baby or babies).tw. (49222)
8. exp Child/ (1477675)
9. (child? or children?).tw. (833828)
10. ADOLESCENT/ (1528060)
11. (adolescen\$ or teenager\$).tw. (165106)
12. p?ediatric\$.tw. (201790)
13. or/4-12 (3016395)
14. and 13 (250)
15. exp Feeding Methods/ (35982)
16. Intubation, Gastrointestinal/ (8055)
17. ((oral or orally or sip or bottle) adj2 (feed\$ or nutrition\$ or nourish\$)).tw. (5213)
18. ((enteral or enteric) adj2 (nutrition\$ or feed\$)).tw. (9280)
19. Duodenostomy/ or Gastrostomy/ or Jejunostomy/ (7854)
20. (gastrostom\$ or jejunostom\$ or gastrojejunostom\$).tw. (9477)
21. ((duoden\$ or gastro\$ or gastric or nas??gastric or nas??-gastric or nas??jejun\$ or nas??duoden\$ or nas??-duoden\$ or jejun\$ or tube?) adj2 (nutrition\$ or feed\$)).tw.

(7917)

22. ((PEG or NG) adj tube?).tw. (770)
23. exp Intensive care/ (18247)
24. (intensive care or ICU).tw. (91420)
25. exp Gastrointestinal motility/ (31800)
26. ((gastr\$ or intestin\$ or gut) adj3 (motil\$ or dysmotil\$ or stimulat\$ or emptying or transit)).tw. (27315)
27. peristalsis.tw. (3489)
28. prokinetic?.tw. (1815)
29. or/15-28 (201338)
30. 14 and 29 (58)
31. limit 30 to english language (43)

Cochrane Central Register of Controlled Trials (CENTRAL)

#1 MeSH descriptor: [Domperidone] explode all trees 174

#2 (domperidon* or gastrocure or r33812 or peridys or nauzelin or domidon or motilium):ti,ab,kw (Word variations have been searched) 400

#3 MeSH descriptor: [Feeding Methods] explode all trees 2754

#4 MeSH descriptor: [Intubation, Gastrointestinal] explode all trees 532

#5 (oral feed* or tube feed* or enteral or enteric):ti,ab,kw (Word variations have been searched) 5564

#6 (gastrostom* or jejunostom* or gastrojejunostom*):ti,ab,kw (Word variations have been searched) 440

#7 MeSH descriptor: [Gastrointestinal Motility] explode all trees 2341

#8 (gastro* motility or gastr* emptying or dysmotility or peristalsis or gastr* transit):ti,ab,kw (Word variations have been searched) 3881

#9 #1 or #2 400

#10 #3 or #4 or #5 or #6 or #7 or #8 10902

#11 #9 and #10 in Trials 88

CRD HTA, DARE and EED database

1. (domperidone) OR (motilium) 25
2. MeSH DESCRIPTOR Feeding Behavior EXPLODE ALL TREES 201
3. MeSH DESCRIPTOR Enteral Nutrition EXPLODE ALL TREES 161
4. MeSH DESCRIPTOR Intubation, Gastrointestinal EXPLODE ALL TREES 36
5. (enteral) OR (enteric) OR (feed) OR (nasogastric) OR (gastrostom*) 475
6. MeSH DESCRIPTOR Gastrointestinal Motility EXPLODE ALL TREES 37
7. (motility) OR (dysmotility) OR (emptying) OR (prokinetic*) OR (peristalsis) 169
8. #2 OR #3 OR #4 OR #5 OR #6 OR #7 829
9. #1 AND #8 12

Grey literature and ongoing trials

1. [FDA](#)
2. [EMA](#)
3. [MHRA](#)
4. [Scottish Medicines Consortium](#)
5. [All Wales Medicine Strategy Group](#)
6. [metaRegister of Controlled Trials \(mRCT\)](#)

7. [ClinicalTrials.gov](https://clinicaltrials.gov)

Manufacturers' websites

[McNeil Products UK](#)

[Zentiva](#)

Evidence selection

The literature search looked for published evidence that investigated using domperidone in children and young people (under 18 years old) being enterally fed to promote tolerance of enteral feeds. No restrictions on study type or publication date were used in the initial search.

Studies in adults, those specifying non-enteral feeding methods, and those without an abstract to review, were excluded. Studies that, from the title and abstract, described using domperidone to treat specific conditions such as dyspepsia, diabetic gastroparesis or gastro-oesophageal reflux disease without reference to enteral feeding or improving feeding tolerance were also excluded from full text review.

This selection process found 1 partially blinded, randomised crossover study relevant to the off-label indication and population of interest. A retrospective look through the initial search results was undertaken to identify any additional relevant case reports, but none was found. Therefore, the single study provided the main evidence for this summary.

Changes after publication

February 2015: Minor maintenance.

September 2014: The following information has become available since this ESUOM was produced:

Domperidone: risks of cardiac side effects - indication restricted to nausea and vomiting, new contraindications, and reduced dose and duration of use.

A European review has confirmed that domperidone is associated with a small increased

risk of serious cardiac side effects. Its use is now restricted to the relief of nausea and vomiting and the dosage and duration of use have been reduced. It should no longer be used for the treatment of bloating and heartburn. Domperidone is now contraindicated in those with underlying cardiac conditions and other risk factors. See the Medicines and Healthcare Products Regulatory Agency [Drug Safety Update May 2014](#) for more information.

About 'Evidence summaries: unlicensed or off-label medicines'

NICE evidence summaries for off-label or unlicensed 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. They 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.

This document provides a summary of the published evidence. The strengths and weaknesses of the identified evidence are critically reviewed within this summary, but this summary is not NICE guidance and does not provide formal practice recommendations.

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