

# Gastroparesis in adults: oral erythromycin

Evidence summary

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[www.nice.org.uk/guidance/esuom13](http://www.nice.org.uk/guidance/esuom13)

## Key points from the evidence

The content of this evidence summary was up-to-date in June 2013. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

## Summary

Only 1 small single-blind, [crossover study](#) (n=13) identified in a [systematic review](#) (5 studies, varying designs, n = 60) found a [statistically significant](#) benefit for erythromycin in the short term for improving symptoms of gastroparesis compared with metoclopramide. The other studies identified in the systematic review did not provide reliable evidence of the effectiveness, safety and tolerability of erythromycin for gastroparesis in either the short or longer term.

**Regulatory status:** Off-label for treating symptoms of gastroparesis.

<p><b>Effectiveness</b></p> <ul style="list-style-type: none"> <li>• Five small studies (n=60), 4 of which reported on symptoms as an outcome.</li> <li>• Only 1 study found a statistically significant benefit of oral erythromycin on symptoms compared with metoclopramide. Another controlled study found no benefit compared with placebo. Two uncontrolled studies found no benefit compared with baseline symptoms.</li> </ul>	<p><b>Safety</b></p> <p>Erythromycin:</p> <ul style="list-style-type: none"> <li>• Can rarely cause serious adverse effects such as hearing loss, allergic reactions, skin reactions, hepatic dysfunction and cardiac arrhythmias.</li> <li>• Is associated with many drug interactions.</li> <li>• Is contraindicated in people with known hypersensitivity, and in those taking astemizole, terfenadine, cisapride, pimozide, ergotamine, dihydroergotamine and simvastatin.</li> </ul>
<p><b>Patient factors</b></p> <ul style="list-style-type: none"> <li>• Gastrointestinal adverse effects, including nausea, vomiting, diarrhoea and abdominal pain, are common with erythromycin.</li> </ul>	<p><b>Cost</b></p> <ul style="list-style-type: none"> <li>• Erythromycin is available in various strengths and formulations with costs ranging from £1.91 to £12.70 for 28 capsules or tablets.</li> </ul>

## Key points

Erythromycin is a macrolide antibiotic that is licensed for treating and preventing infections. It does not have UK marketing authorisation for treating gastroparesis and so this indication is an off-label use of erythromycin.

Managing gastroparesis centres on nutrition and fluid balance. If pharmacological treatment is required, metoclopramide, domperidone or erythromycin may be considered

as motility agents.

There is limited evidence reviewing the efficacy of oral erythromycin in people with gastroparesis. One systematic review ([Maganti et al. 2003](#)) including 5 studies (n=60), and 1 retrospective chart review (n=25) were identified.

Of the 5 studies in the systematic review, only 4 reported on change in symptom scores, and none assessed symptom improvement as the primary end point. Of the 4 studies which reported symptom scores, 1 was a double-blind, placebo-controlled, crossover study, 1 was a single-blind, active-controlled (metoclopramide) crossover study, and 2 were open-label uncontrolled studies.

Erythromycin improved measures of gastric emptying compared with baseline in all the studies. However, of the 4 studies that reported on symptoms, 1 found that oral erythromycin did not statistically significantly improve symptoms compared with placebo ([Samsom et al. 1997](#)); 1 study found statistically significant improvement compared with metoclopramide ([Erbas et al. 1993](#)), and 2 open-label uncontrolled studies found no statistically significant improvement in symptoms compared with baseline ([Richards et al. 1993](#) and [Ramirez et al. 1994](#)). One of the uncontrolled studies found a statistically significant improvement in global assessment score ([Richards et al. 1993](#)).

The retrospective chart review ([Dhir and Richter 2004](#)) included a series of patients with dyspepsia and gastroparesis treated with a low-bulk diet and 50 to 100 mg oral erythromycin suspension 3 times a day and at bedtime. The chart review collected data on responses at 6 to 8 weeks; longer term responses were collected by telephone follow up. Of the 25 patients, 18 were assessed by chart review, and 18 had longer term telephone follow up. Fifteen out of 18 patients had "some" (<50% of baseline) or "dramatic" (>50% of baseline) reduction in symptoms on the 6 to 8 week chart review. Twelve out of 18 patients had "some" or "dramatic" improvement in the longer term (up to 2 years) follow up. Retrospective chart reviews and case series rarely provide evidence which is sufficiently strong to confidently guide clinical practice.

Erythromycin is often associated with gastrointestinal adverse effects, including abdominal discomfort, nausea, vomiting and diarrhoea. Rare adverse effects include hearing loss, allergic reactions (including anaphylaxis), skin reactions (including erythema multiforme and Stevens-Johnson syndrome), hepatitis and hepatic dysfunction, cardiac arrhythmias and pseudomembranous colitis. Erythromycin is contraindicated in people with known hypersensitivity, and in those taking certain medications including astemizole, terfenadine,

cisapride and pimozone (increased risk of cardiotoxicity), ergotamine and dihydroergotamine (increased risk of ergot toxicity), and simvastatin (increased risk of myopathy and rhabdomyolysis).

Erythromycin may interact with various other medications, including increasing serum concentrations of drugs metabolised by the cytochrome P450 system. The relevant [summaries of product characteristics](#) contain more information on drug interactions and adverse effects of erythromycin.

#### **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**

Erythromycin is a macrolide antibiotic that is licensed for treating and preventing infections.

### **Regulatory status of erythromycin**

Erythromycin does not have marketing authorisation in the UK for treating gastroparesis and so this is an off-label use of the drug.

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 erythromycin outside its authorised indications.

## Evidence statements

- One systematic review ([Maganti et al. 2003](#)) was identified that reviewed 5 clinical studies evaluating the efficacy of oral erythromycin for the symptomatic relief of gastroparesis.
- One study was a double-blind, placebo-controlled crossover study ([Samsom et al. 1997](#)); 1 was a single-blind, active-controlled (metoclopramide) crossover study ([Erbas et al. 1993](#)); and 3 were open-label uncontrolled studies ([Richards et al.1993](#), [Ramirez et al. 1994](#) and [Fiorucci et al. 1994](#)). They included a total of 60 people with gastroparesis associated with diabetes (2 studies) diabetes or of unknown cause (idiopathic) (1 study), systemic sclerosis (1 study) or surgery (1 study).
- Oral erythromycin was administered at dosages ranging from 125 mg 3 times daily to 500 mg 4 times daily, for between 2 and 4 weeks.
- When the original research papers of the 5 included studies were reviewed, only 4 report on change in symptom scores. The remaining study only reports the effect of a single intravenous erythromycin infusion on gastric and gallbladder activity and gastric motility. Of the 4 studies that reported on symptoms, 1 found that oral erythromycin did not statistically significantly improve symptoms compared with placebo ([Samsom et al. 1997](#)); 1 study found statistically significant improvement compared with metoclopramide ([Erbas et al. 1993](#)); and 2 open-label uncontrolled studies found no statistically significant improvement in symptoms compared with baseline ([Richards et al.1993](#) and [Ramirez et al. 1994](#)).
- For disease-orientated outcomes, the controlled studies found that oral erythromycin statistically significantly improved gastric emptying compared with placebo, and both erythromycin and metoclopramide improved gastric emptying parameters.
- The 5 studies included in the systematic review were small including 14 or fewer participants in each, and all were of poor methodological quality with high risk of bias. They provide limited evidence for the efficacy of oral erythromycin, and no reliable evidence for safety and tolerability in either the short or longer term.

- Erythromycin is often associated with gastrointestinal adverse effects, including abdominal discomfort, nausea, vomiting and diarrhoea. Rare adverse effects include hearing loss, allergic reactions (including anaphylaxis), skin reactions (including erythema multiforme and Stevens-Johnson syndrome), hepatitis and hepatic dysfunction, cardiac arrhythmias and pseudomembranous colitis. Erythromycin has various drug interactions and contraindications.

## Summary of the evidence

### Efficacy

One systematic review ([Maganti et al. 2003](#)) was identified. It reviewed studies evaluating the efficacy of oral erythromycin for the symptomatic relief of gastroparesis.

Four of the 5 studies in the review investigated the effect of oral erythromycin on symptoms, although none of these assessed symptom improvement as the primary end point. One study was a double-blind, placebo-controlled, crossover study ([Samsom et al. 1997](#)); 1 was a single-blind, active-controlled (metoclopramide), crossover study ([Erbas et al. 1993](#)); and 2 were open-label uncontrolled studies ([Richards et al. 1993](#), and [Ramirez et al. 1994](#)). The included populations were people with gastroparesis associated with diabetes (2 studies), diabetes or of unknown cause (idiopathic) (1 study), and surgery (1 study).

Erythromycin was administered orally with dosages ranging from 125 mg 3 times daily to 500 mg 4 times daily, and treatment periods ranging from 2 to 4 weeks. All studies were small including 14 or fewer participants in each, and all were of poor methodological quality with high risk of bias. The studies included a total of 60 participants.

Of the 4 studies that reported on symptoms, 1 found that oral erythromycin did not statistically significantly improve symptoms compared with placebo ([Samsom et al. 1997](#)); 1 found statistically significant improvement compared with metoclopramide ([Erbas et al. 1993](#)); and 2 open-label uncontrolled studies found no statistically significant improvement in symptoms compared with baseline ([Richards et al. 1993](#) and [Ramirez et al. 1994](#)). Erythromycin improved measures of gastric emptying compared with baseline in all studies. In the 2 controlled studies, oral erythromycin statistically significantly improved gastric emptying compared with placebo and both erythromycin and metoclopramide improved gastric emptying parameters.

**Table 1 Summary of the studies included in the [Maganti et al. \(2003\)](#) systematic review**

	Intervention	Control	Analysis
<b><a href="#">Samsom et al. (1997)</a> double-blind, crossover study; n = 12</b>			
	<b>Erythromycin 250 mg, 3 times daily</b>	<b>Placebo</b>	
Mean post-treatment symptom scores	1.53±0.67	1.81±0.86	p=0.16 Statistically significant improvement with erythromycin was seen in 7 people with postprandial antral hypomotility (baseline score 2.07±0.86 to 1.52±0.63, p=0.018)
Effect on gastric activity	Fasting motor activity: 86.2±25.3 minutes	Fasting motor activity: 118.9±46.0 minutes	p=0.03
	Phase II periods: 48.5±19.4 minutes	Phase II periods: 68.7±23.5 minutes	p<0.05
	Phase III periods: 6.3±1.7 minutes	Phase III periods: 5.2±1.4 minutes	p<0.05
Adverse effects			No clinical or biochemical adverse effects were observed during erythromycin treatment
<b><a href="#">Erbas et al. (1993)</a> single-blind, crossover study; n = 13</b>			
	<b>Erythromycin 250 mg, 3 times daily</b>	<b>Metoclopramide 10 mg, 3 times daily</b>	

Median post-treatment symptom scores (range)	2 (0–5)	3 (0–11)	p<0.05
Effect on gastric activity	T <sub>1/2</sub> reduced from 110 minutes (77–120) to 55 minutes (28–115) (50% decrease)	T <sub>1/2</sub> reduced from 110 minutes (77–120) to 67 minutes (5–115) (39% decrease)	Both treatments significantly reduced T <sub>1/2</sub> compared with baseline (p value not reported), but there was no statistically significant difference between groups
Adverse effects			No adverse effects were reported after erythromycin, although with metoclopramide 2 people experienced weakness, sedation and leg cramps, 1 person had palpitations and 1 other had drowsiness
<b>Richards et al. (1993) open-label, uncontrolled study</b>			
	<b>Erythromycin 250 mg to 500 mg, 4 times daily</b>	<b>NA</b>	
Inclusion	n=14		
Efficacy	n=10		
Mean post-treatment symptom scores	Baseline: 30±16 4 weeks: 24±13		p=0.2

Mean global assessment score	Baseline: 7.2±2.1 4 weeks: 4.7±2.9		p=0.03
Effect on gastric activity: mean percentage of food retained in stomach after 2 hours	Baseline: 85% (±11) 4 weeks: 48% (±21)		p<0.01
Adverse effects			Four people withdrew from the study (2 because of rash, 1 with cramps and vomiting, and 1 because of other medical problems). Of the 10 who completed, 3 required dose reduction because of gastrointestinal complaints (nausea and vomiting in 1, cramps and abdominal pain in 2)
<b>Ramirez et al. (1994) open-label, uncontrolled study; n = 9</b>			
	<b>Erythromycin 150 mg, 3 times daily (range 125 mg to 250 mg, 3 times daily)</b>	<b>NA</b>	
Mean total symptom score	Baseline: 9.2±0.5 2 weeks: 7.8±0.6		p value not reported but stated to be not significant

Adverse effects			No adverse effects reported
Abbreviations: NA, not applicable; SR systematic review; $T_{1/2}$ , half time of gastric emptying.			

## Safety

The studies included in the systematic review do not provide reliable evidence of the risk of adverse effects with erythromycin.

The [summaries of product characteristics](#) for erythromycin state that the drug is contraindicated in people with known hypersensitivity, and in those taking certain medications including astemizole, terfenadine, cisapride and pimozide (increased risk of cardiotoxicity), ergotamine and dihydroergotamine (increased risk of ergot toxicity), and simvastatin (increased risk of myopathy and rhabdomyolysis).

Caution is advised when using erythromycin in people with hepatic impairment or in those receiving potentially hepatotoxic agents (hepatic dysfunction has been infrequently reported); those with myasthenia gravis (weakness may be aggravated); and in seriously ill people receiving erythromycin concomitantly with statins (rhabdomyolysis has been reported). The [summaries of product characteristics](#) also warn that, as with other broad spectrum antibiotics, pseudomembranous colitis has been rarely reported with erythromycin. Erythromycin may interact with various other medications, including increasing serum concentrations of drugs metabolised by the cytochrome P450 system (including acenocoumarol, carbamazepine, ciclosporin, digoxin, midazolam, omeprazole, phenytoin, sildenafil, tacrolimus, theophylline and valproate). The [summaries of product characteristics](#) for erythromycin describe common adverse effects including nausea, abdominal discomfort, vomiting and diarrhoea.

There have been isolated reports of reversible hearing loss occurring with high doses of erythromycin or in people with renal insufficiency.

The following adverse effects have been rarely reported:

- allergic reactions, including anaphylaxis

- skin reactions, including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis
- hepatitis and hepatic dysfunction
- cardiac arrhythmias and reports of chest pain and palpitations.

The relevant [summaries of product characteristics](#) contain more information on drug interactions and adverse effects of erythromycin.

## Cost effectiveness and cost

No cost-effectiveness studies of erythromycin for use in gastroparesis were identified.

The [NHS Electronic Drug Tariff \(May 2013\)](#) lists the price for erythromycin oral capsules or tablets as follows:

- erythromycin 250 mg gastro-resistant capsules, 28-tablet pack: £12.70
- erythromycin 250 mg gastro-resistant tablets, 28-tablet pack: £1.91
- erythromycin ethyl succinate 500 mg tablets, 28-tablet pack: £10.78
- erythromycin stearate 250 mg tablets, 100-tablet pack: £18.20
- erythromycin stearate 500 mg tablets, 100-tablet pack: £36.40.

## Relevance to NICE guidance programmes

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

Erythromycin has been reviewed as a motility agent in the following clinical guidelines:

- [Type 2 diabetes: the management of type 2 diabetes](#) (a partial update of CG66) (NICE clinical guideline 87) recommends considering a trial of metoclopramide, domperidone or erythromycin for an adult with gastroparesis, with referral to specialist services if the diagnosis is in doubt or there is persistent or severe vomiting.

- [Nutrition support in adults](#) (NICE clinical guideline 32) recommends consideration of a motility agent for people in intensive or acute care settings who have delayed gastric emptying, are not tolerating enteral tube feeding, and who have no rectifiable pharmacological cause or suspicion of gastrointestinal obstruction. Following review of the available evidence, the [full guideline](#) concludes that erythromycin (and metoclopramide) appears to be effective in improving gastric motility and may improve tolerance to enteral feeds for a limited period, although the available studies do not provide evidence of benefit for important long-term clinical end points. Caution is recommended in the intensive care population because of potential drug interactions and adverse effects.

## Intervention and alternatives

[Erythromycin](#) is a macrolide antibiotic that is used to treat and prevent infections. It is effective for treating certain infections of the upper and lower respiratory tract, ear, eye, oral cavity, skin and soft tissue, gastrointestinal tract and genitourinary tract, and for treating osteomyelitis. It is also used for prophylaxis in pre- and post-operative trauma, burns and rheumatic fever.

Erythromycin is available in various oral formulations including tablets, capsules and oral suspension at strengths of 125 mg (oral suspensions only), 250 mg and 500 mg. Erythromycin tablets and capsules are enteric coated; erythromycin stearate tablets (Erythrocin 250 and 500) and erythromycin ethylsuccinate tablets (Erythroped A 500) and suspension are less susceptible to the adverse effect of gastric acid. The usual dose in adults is 1–2 g daily in divided doses, with up to 4 g daily taken in severe infections.

## Condition

A practice guideline published in *The American Journal of Gastroenterology*, [Clinical guideline: management of gastroparesis](#), defines gastroparesis as a syndrome of objectively measured delayed gastric emptying in the absence of mechanical obstruction, with key symptoms of early satiety, postprandial fullness, nausea, vomiting, bloating and upper abdominal pain. The majority of cases are idiopathic (36%), due to diabetes (29%) or post-surgical (13%).

## Alternative treatment options

The management of gastroparesis centres on nutrition and fluid balance. For pharmacological management, the [Clinical guideline: management of gastroparesis](#) and the NICE clinical guideline on [type 2 diabetes – newer agents](#) recommend that metoclopramide, domperidone or erythromycin may be considered as motility agents. The NICE clinical guideline on [nutrition support in adults](#) advises that metoclopramide or erythromycin may be considered in intensive or acute care settings. Other management approaches include the procedure [gastroelectrical stimulation for gastroparesis](#), guidance on which is currently being updated by the NICE interventional procedures team.

The [British National Formulary](#) currently states that metoclopramide and domperidone may be used for treating gastroparesis in people with diabetic neuropathy, and that in rare cases when these anti-emetics are not beneficial, erythromycin (especially intravenous) may be useful. The BNF does not state that that use of erythromycin for this indication is off label.

## Evidence review: efficacy

One [systematic review](#) was identified ([Maganti et al. 2003](#)) that included clinical studies evaluating the efficacy of oral erythromycin for the symptomatic relief of gastroparesis. Only studies including assessment of symptoms as an end point were included. Symptom improvement was defined as a 25% or greater decrease in total symptom score. A total of 35 "clinical trials" evaluating erythromycin in gastroparesis were identified, 5 of which were stated as including assessment of symptoms as an end point, although none had symptom improvement as the primary end point. These 5 small studies were reported individually; meta-analysis was not undertaken and it is not reported whether the authors considered this.

The study by [Samsom et al. \(1997\)](#) was a double-blind, [crossover study](#) in 12 people with type 1 diabetes and dyspepsia. Participants were assigned to 2 weeks' oral erythromycin stearate (250 mg, 3 times daily) or placebo followed by a 1-week washout then crossover to 2 weeks of the alternative. Symptoms (early satiety, fullness, abdominal pain, bloating, nausea and vomiting) were recorded daily by participants in a symptom diary using a 4-point Likert scale. There was no [statistically significant](#) difference in mean symptom scores between the erythromycin and placebo groups ( $1.53 \pm 0.67$  compared with  $1.81 \pm 0.86$ ;  $p=0.16$ ). Individual symptom scores were not presented.

Ambulatory antroduodenal manometry was performed at the end of each 2-week treatment period. On fasting assessments, erythromycin statistically significantly decreased the duration of gastric motor activity ( $86.2 \pm 25.3$  compared with  $118.9 \pm 46.0$  minutes;  $p=0.03$ ), decreased phase II periods ( $48.5 \pm 19.4$  compared with  $68.7 \pm 23.5$  minutes;  $p < 0.05$ ), and increased phase III periods ( $6.3 \pm 1.7$  compared with  $5.2 \pm 1.4$  minutes;  $p < 0.05$ ). There was no statistically significant increase in the number of phase III events. Postprandially, erythromycin statistically significantly increased the number of antral contractions ( $p < 0.01$ ) and antral motility index ( $p < 0.03$ ).

No adverse effects were observed in the study.

The study by [Erbas et al. \(1993\)](#) was a single-blind crossover study comparing oral erythromycin (250 mg, 3 times daily) with metoclopramide (10 mg, 3 times daily) in 13 people with diabetes and gastroparesis. Treatment was for 3 weeks followed by a 3-week washout then crossover to the alternative. Symptoms (gastric retention, early satiety, abdominal pain, bloating, nausea and vomiting, constipation, diarrhoea and anorexia) were assessed on a 4-point Likert scale. Median baseline symptom score was 8 (range 2 to 11) out of a possible total of 24 points, with a higher score indicating more severe symptoms. Symptom scores improved in both treatment groups, but erythromycin improved symptoms statistically significantly more from baseline than metoclopramide (median symptom score 2 points [range, 0–5] compared with 3 points [0–11] respectively;  $p < 0.05$ ).

The half-time of gastric emptying ( $T_{1/2}$ ) was assessed at baseline and after each treatment using a radiolabeled meal. Both treatments significantly improved gastric emptying.  $T_{1/2}$  at baseline was a median 110 minutes (77–120) which reduced to 55 minutes (28–115) after 3 weeks of erythromycin (50% decrease), and to 67 minutes (5–115) after 3 weeks of metoclopramide (39% decrease). When compared with baseline values, the authors report that significant differences in gastric emptying parameters were found after both erythromycin and metoclopramide treatment compared with baseline, but there was no difference between the groups. No statistical values were reported in the original research paper.

No adverse effects were reported after erythromycin, although with metoclopramide 2 people experienced weakness, sedation and leg cramps, 1 had palpitations and 1 other had drowsiness.

The study by [Richards et al. \(1993\)](#) was open-label and uncontrolled evaluating 4 weeks'

oral erythromycin (500 mg, 4 times daily) in 10 people with idiopathic gastroparesis and 4 people with diabetic gastroparesis. Oral therapy followed an initial dose of intravenous erythromycin. After completion of the 4-week treatment period, participants were able to enter a long-term treatment study.

Only 10 of the 14 participants completed the study; 4 withdrew (2 because of rash, 1 with cramps and vomiting, and 1 because of other medical problems). Analysis was per protocol. Symptoms (early satiety, abdominal pain, bloating, nausea, vomiting, heartburn and anorexia) and global wellbeing were assessed at baseline and at the end of the treatment period (plus every 8 weeks for those who continued oral erythromycin in the long-term study) using a 10-point Likert scale with higher scores indicating more severe symptoms. Erythromycin was associated with a statistically significant improvement in the global assessment score (mean score decrease from  $7.2 \pm 2.1$  to  $4.7 \pm 2.9$ ;  $p=0.03$ ) but did not statistically significantly improve symptom score (mean score decrease from  $30 \pm 16$  to  $24 \pm 13$ ;  $p=0.2$ ). The systematic review reports that 2 people experienced a 25% or greater reduction in their symptoms, a result that was not identified in the original research paper. Gastric emptying was assessed at baseline, after the initial dose of intravenous erythromycin and after 4 weeks of oral treatment using radioisotope imaging. The percentage of radiolabeled meal retained in the stomach at 2 hours decreased from  $85 \pm 11\%$  at baseline to  $48 \pm 21\%$  after 4 weeks ( $p < 0.01$ ). Of the 10 people who completed the study and continued with oral erythromycin, 5 experienced sufficient symptom relief to continue in the longer term (average 8.4 months). No toxicity was experienced by these 5 people who continued erythromycin. The other 5 people stopped using erythromycin because of no or inadequate improvement in symptoms. No attempt was made to apply statistical analysis to the longer-term symptom scores, although the authors report that in general scores did not change much from those recorded at the end of the 4-week trial.

The study by [Ramirez et al. \(1994\)](#) was open-label and uncontrolled evaluating 2 weeks' erythromycin ethylsuccinate oral suspension (125 to 250 mg, 3 times daily, depending on the optimal tolerated dose) in 9 people with gastroparesis after truncal vagotomy and antrectomy for refractory peptic ulcer disease. Oral therapy followed an initial trial with a single dose of intravenous and/or oral erythromycin. The reported results are for the 2-week oral trial. Symptoms (postprandial fullness, abdominal pain, nausea and vomiting) were assessed on a 4-point Likert scale (maximum score of 12) at baseline and after treatment. Erythromycin did not significantly improve symptoms in the group overall (mean symptom score  $9.2 \pm 0.5$  at baseline compared with  $7.8 \pm 0.6$  after treatment;  $p$  value not reported). In the 3 people who did show symptom improvement, their score decreased from a mean  $11.0 \pm 0.3$  at baseline to  $5.7 \pm 0.3$  after treatment ( $p < 0.01$ ). Individual symptom

scores were not reported.

There were reported to have been no adverse effects during the study.

The study by [Fiorucci et al. \(1994\)](#) was reported to be an open-label uncontrolled study evaluating 4 weeks' oral erythromycin (250 mg, 3 times daily) in 12 people with systemic sclerosis and gastroparesis. The publication referenced by [Maganti et al. \(2003\)](#) evaluated only a single intravenous erythromycin infusion and reported only the effect of gastric and gallbladder activity and gastric motility. None of the results in the referenced publication are consistent with those reported in the systematic review; it is unknown whether a 4-week oral study followed the intravenous trial and where the symptomatic results in the report of this study in the systematic review were published.

In addition to the systematic review, a small retrospective chart review ([Dhir and Richter 2004](#)) was identified that included 25 people (mean age  $49 \pm 18$  years, range 19 to 86 years) with impaired gastric emptying and dyspepsia symptoms. All participants received erythromycin oral suspension 50-100 mg before each meal and at bedtime. Symptoms at baseline and at short-term follow-up (6–8 weeks) were reported retrospectively from patient charts. Symptoms on long-term follow-up were evaluated through telephone interview. Symptoms were assessed as worse, unchanged, some improvement (<50% of baseline) and dramatic improvement (>50% of baseline) at both short- and long-term follow-up. Of the 18 people who were followed up in the short term, 15 (83%) experienced symptom improvement with erythromycin, of whom 12 (66%) reported dramatic improvement. Three people (17%) reported no improvement or worsening of symptoms and differences reported were all statistically significant ( $p=0.005$ ). At the telephone follow-up, 12 of 18 people (67%) had experienced symptom improvement during long-term ( $11 \pm 7$  months, range 1 to 29 months) erythromycin use compared with 6 (33%) who experienced no improvement or worsening of symptoms ( $p=0.16$ ). Only 3 people (17%) were still using erythromycin at the time of the telephone follow-up. These 3 people reported complete symptom resolution. The most common reason for stopping erythromycin was failure to completely relieve symptoms.

During short-term follow-up, 1 person stopped erythromycin because of severe nausea and vomiting. In the longer term, 5 people reported adverse effects of erythromycin including headaches, nausea, abdominal cramps and loose bowel movements.

## Evidence review: safety

The studies included in the systematic review and the retrospective chart review do not provide reliable evidence of the risk of adverse effects with erythromycin.

The [summaries of product characteristics](#) for erythromycin state that the drug is contraindicated in people with known hypersensitivity, and in those taking certain medications including astemizole, terfenadine, cisapride and pimozide (increased risk of cardiotoxicity), ergotamine and dihydroergotamine (increased risk of ergot toxicity), and simvastatin (increased risk of myopathy and rhabdomyolysis).

Caution is advised when using erythromycin in people with hepatic impairment or in those receiving potentially hepatotoxic agents (hepatic dysfunction has been infrequently reported); those with myasthenia gravis (weakness may be aggravated); and in seriously ill people receiving erythromycin concomitantly with statins (rhabdomyolysis has been reported). The [summaries of product characteristics](#) also warn that, as with other broad spectrum antibiotics, pseudomembranous colitis has been rarely reported with erythromycin. Erythromycin may interact with various other medications, including increasing serum concentrations of drugs metabolised by the cytochrome P450 system (including acenocoumarol, carbamazepine, ciclosporin, digoxin, midazolam, omeprazole, phenytoin, sildenafil, tacrolimus, theophylline and valproate). The [summaries of product characteristics](#) describe common adverse effects including nausea, abdominal discomfort, vomiting and diarrhoea.

There have been isolated reports of reversible hearing loss occurring with high doses of erythromycin or in people with renal insufficiency.

The following adverse effects have been rarely reported:

- allergic reactions, including anaphylaxis
- skin reactions, including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis
- hepatitis and hepatic dysfunction
- cardiac arrhythmias and reports of chest pain and palpitations.

The relevant [summaries of product characteristics](#) contain more information on drug

interactions and adverse effects of erythromycin.

## Evidence review: economic issues

### Cost effectiveness

No cost-effectiveness studies of erythromycin for use in gastroparesis were identified.

### Cost

The [NHS Electronic Drug Tariff \(May 2013\)](#) lists the price for erythromycin oral capsules or tablets as follows:

- erythromycin 250 mg gastro-resistant capsules, 28-tablet pack: £12.70
- erythromycin 250 mg gastro-resistant tablets, 28-tablet pack: £1.91
- erythromycin ethyl succinate 500 mg tablets, 28-tablet pack: £10.78
- erythromycin stearate 250 mg tablets, 100-tablet pack: £18.20
- erythromycin stearate 500 mg tablets, 100-tablet pack: £36.40.

### Current drug usage

A total of 2,344,220 items of erythromycin oral preparations were dispensed in England in 2012 at a total cost of £11,525,854. It is not known for which indications these items were prescribed.

## Evidence strengths and limitations

Only 1 systematic review was identified ([Maganti et al. 2003](#)) that reviewed studies evaluating the efficacy of oral erythromycin for the symptomatic relief of gastroparesis. All of the 5 studies identified by the [systematic review](#) were small, methodologically flawed and carried a high risk of [bias](#). The study by [Samsom et al. \(1997\)](#) was a double-blind, placebo-controlled [crossover study](#). This study was considered in the NICE clinical

guideline on [type 2 diabetes – newer agents](#), but was excluded for methodological reasons. The study by [Erbas et al. \(1993\)](#) was a single-blind, active-controlled (metoclopramide), crossover study. This found a statistically significant beneficial effect on symptoms from using erythromycin compared with metoclopramide. The authors, however, did not report if the [statistically significant](#) benefit translated into a [clinically important](#) difference. The small numbers of participants included in these 2 controlled studies (n=12 and n=13 respectively) suggest that it is likely that these studies may not have been sufficiently powered to detect differences between the interventions.

No study identified reliable evidence for the safety and tolerability of erythromycin in either the short or longer term.

The studies included in the systematic review had several limitations. The treated populations had gastroparesis caused by various conditions including diabetes, unknown cause (idiopathic), systemic sclerosis, or surgery. The dose of oral erythromycin differed in the studies, with dosages ranging from 125 mg 3 times daily to 500 mg 4 times daily, and treatment periods ranging from 2 to 4 weeks.

The systematic review searched only one database (MEDLINE) meaning that important relevant trials not indexed on this database could have been missed. In addition, only a descriptive narrative of the included studies was carried out and no statistical analysis was performed, although this may have been appropriate given the differences in the included studies. The review was poorly reported with some results presented that were not published in the original research papers.

A literature search found an additional retrospective chart review that assessed the effect of oral erythromycin on dyspepsia symptoms in 25 people with impaired gastric emptying. Retrospective chart reviews and case series rarely provide evidence which is on its own sufficiently strong to guide clinical practice.

## Summary for patients

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

## References

British National Formulary (2013) [Diabetic neuropathy](#) [online; accessed 15 April 2013]

Camilleri M, Parkman HP, Shafi MA et al. (2013) Clinical guideline: management of gastroparesis. The American Journal of Gastroenterology 108: 18–37

Dhir R, Richter J (2004) Erythromycin in the short and long term control of dyspepsia symptoms in patients with gastroparesis. Journal of Clinical Gastroenterology 38(3): 237–42

Erbas T, Varoglu E, Erbas B et al. (1993) Comparison of metoclopramide and erythromycin in the treatment of diabetic gastroparesis. Diabetes Care 16: 1511–14

Fiorucci S, Distrutti E, Bassotti G et al. (1994) Effect of erythromycin administration on upper gastrointestinal motility in scleroderma patients. Scandinavian Journal of Gastroenterology 29: 807–13

Maganti K, Onyemere K, Jones MP (2003) Oral erythromycin and symptomatic relief of gastroparesis: a systematic review. American Journal of Gastroenterology 98: 259–63

National Institute for Health and Clinical Excellence (2004) Gastroelectrical stimulation for gastroparesis. NICE interventional procedure guidance 103

National Institute for Health and Clinical Excellence (2006) Nutrition support in adults. NICE clinical guideline 32

National Institute for Health and Clinical Excellence (2009) Type 2 diabetes – newer agents. NICE clinical guideline 87

Ramirez B, Eaker EY, Drane WE et al. (1994) Erythromycin enhances gastric emptying in patients with gastroparesis after vagotomy and antrectomy. Digestive Diseases and Sciences 39: 2295–300

Richards RD, Davenport K, McCallum RW (1993) The treatment of idiopathic and diabetic gastroparesis with acute intravenous and chronic oral erythromycin. The American Journal of Gastroenterology 88: 203–7

Sansom M, Jebbink RJ, Akkermans LM et al. (1997) Effects of oral erythromycin on fasting and postprandial antroduodenal motility in patients with type I diabetes, measured with an ambulatory manometric technique. Diabetes Care 20: 129–34

# Development of this evidence summary

This evidence summary was developed for NICE by Bazian Ltd. The [interim 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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Bazian Ltd

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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:

- [NICE Evidence](#)
- [NICE](#)
- [Euroscan](#)
- Broad internet search: [Google](#) e.g.: (~guideline OR ~algorithm) uk gastroparesis OR "gastrointestinal motility" "erythromycin" filetype:pdf
- [Scirus](#)

## MEDLINE (via Ovid)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

- 
1. Gastroparesis/ (1009)
  2. exp Gastrointestinal Motility/ (31668)
  3. gastroparesis.tw. (1438)
  4. ((gut or gastr\$ or intestin\$) adj3 (motil\$ or stimulat\$ or emptying or volume)).tw. (25995)
  5. (prokinetic? or motilin).tw. (3274)
  6. or/1-5 (47859)

7. exp Erythromycin/ (20430)
8. (erythromycin or erythrocin).tw. (16475)
9. or/7-8 (28591)
10. 6 and 9 (770)
11. exp review/ (1762473)
12. (scisearch or psychinfo or psycinfo or medlars or embase or psychlit or psychlit or cinahl or pubmed or medline).ti,ab,sh. (72606)
13. ((hand adj2 search\$) or (manual\$ adj2 search\$)).ti,ab,sh. (6307)
14. ((electronic or bibliographic or computeri?ed or online) adj4 database\$).ti,ab. (14079)
15. (pooling or pooled or mantel haenszel).ti,ab,sh. (46568)
16. (peto or dersimonian or der simonian or fixed effect).ti,ab,sh. (2711)
17. or/12-16 (124050)
18. 11 and 17 (55034)
19. Meta Analysis/ (38447)
20. (meta-analys\$ or meta analys\$ or metaanalys\$).ti,ab,sh. (67979)
21. ((systematic\$ or quantitativ\$ or methodologic\$) adj5 (review\$ or overview\$ or synthesis\$)).ti,ab,sh. (54721)
22. (integrative research review\$ or research integration).ti,ab,sh. (83)
23. or/19-22 (105814)
24. 18 or 23 (133970)
25. clinical trials, phase iv/ or clinical trials, phase iii/ or randomized controlled trials/ or multicenter studies/ (239776)
26. (random\$ or placebo\$ or ((singl\$ or double\$ or triple\$ or treble\$) and (blind\$ or mask\$))).ti,ab,sh. (881775)

27. 25 or 26 (978772)
28. (animal\$ not human\$).sh. (3697331)
29. 27 not 28 (873244)
30. (cost\$ or economic\$).tw. (428385)
31. 24 or 29 or 30 (1338733)
32. 10 and 31 (200)
33. (child\$ or neonat\$ or infant\$).ti. (737652)
34. 32 not 33 (167)

## Embase (via Ovid)

Database: Embase <1988 to 2013 March 27>

Search Strategy:

---

1. Gastroparesis/ (3010)
2. exp Gastrointestinal Motility/ (17703)
3. gastroparesis.tw. (2156)
4. ((gut or gastr\$ or intestin\$) adj3 (motil\$ or stimulat\$ or emptying or volume)).tw. (24434)
5. Prokinetic Agent/ (2713)
6. (prokinetic? or motilin).tw. (3717)
7. or/1-6 (39489)
8. exp Erythromycin/ (44780)
9. Erythromycin Stearate/ (245)

10. (erythromycin or erythrocin).tw. (15802)
11. or/8-10 (48214)
12. 7 and 11 (1759)
13. exp review/ (1749103)
14. (scisearch or psychinfo or psycinfo or medlars or embase or psychlit or psyclit or cinahl or pubmed or medline).ti,ab,sh. (90738)
15. ((hand adj2 search\$) or (manual\$ adj2 search\$)).ti,ab,sh. (7500)
16. ((electronic or bibliographic or computeri?ed or online) adj4 database\$).ti,ab. (18342)
17. (pooling or pooled or mantel haenszel).ti,ab,sh. (53580)
18. (peto or dersimonian or der simonian or fixed effect).ti,ab,sh. (3441)
19. or/14-18 (150582)
20. 13 and 19 (58085)
21. Meta Analysis/ (69811)
22. (meta-analys\$ or meta analys\$ or metaanalys\$).ti,ab,sh. (100151)
23. ((systematic\$ or quantitativ\$ or methodologic\$) adj5 (review\$ or overview\$ or synthesis\$)).ti,ab,sh. (94215)
24. (integrative research review\$ or research integration).ti,ab,sh. (88)
25. or/21-24 (165556)
26. 20 or 25 (193552)
27. clinical trials, phase iv/ or clinical trials, phase iii/ or randomized controlled trials/ or multicenter studies/ (32839)
28. (random\$ or placebo\$ or ((singl\$ or double\$ or triple\$ or treble\$) and (blind\$ or mask\$))).ti,ab,sh. (1005043)
29. 27 or 28 (1008655)

30. (animal\$ not human\$).sh. (2488267)
31. 29 not 30 (910462)
32. (cost\$ or economic\$).tw. (483579)
33. 26 or 31 or 32 (1459226)
34. 12 and 33 (442)
35. (child\$ or neonat\$ or infant\$).ti. (580915)
36. 34 not 35 (390)
37. limit 36 to exclude medline journals (43)
38. limit 37 to english language (34)

## **Cochrane Central Register of Controlled Trials (CENTRAL)**

Date Run: 28/03/13 15:00:53.727

### ID Search Hits

#1 MeSH descriptor: [Gastroparesis] explode all trees 96

#2 MeSH descriptor: [Gastrointestinal Motility] explode all trees 2336

#3 gastroparesis or (gastr\* next/2 motility) or (gastr\* next/2 emptying):ti,ab,kw (Word variations have been searched) 2920

#4 prokinetic\* or "motilin":ti,ab,kw (Word variations have been searched) 535

#5 #1 or #2 or #3 or #4 3591

#6 MeSH descriptor: [Erythromycin] this term only 882

#7 "erythromycin" or "erythrocin":ti,ab,kw (Word variations have been searched) 1555

#8 #6 or #7 1555

#9 #5 and #8 in Trials 170

## CRD HTA, DARE and EED database

(gastroparesis) OR (gastr\* emptying) OR (gastr\* motility) OR (prokinetic) OR (motilin) AND (erythromycin)

## Grey literature and ongoing trials

- [FDA](#)
- [EMA](#)
- [MHRA](#)
- [Scottish Medicines Consortium](#)
- [All Wales Medicine Strategy Group](#)
- [metaRegister of Controlled Trials \(mRCT\)](#)
- [ClinicalTrials.gov](#)

## Manufacturers' websites

There are a large number of generic and branded erythromycin formulations available. See the relevant [summaries of product characteristics](#) for links to the various manufacturers.

## Evidence selection

This evidence summary has included studies that have investigated the efficacy of oral erythromycin for treating gastroparesis of any underlying cause in adults.

Studies have been excluded if their aim was to investigate the effect of erythromycin on gastric emptying and gastrointestinal transit times rather than treating symptoms of gastroparesis. This has included studies comparing pre- or post-operative doses of erythromycin as prophylaxis in people undergoing abdominal surgery to investigate whether this has an effect on outcomes such as gastric volume or emptying or gastrointestinal symptoms. Studies focusing on whether erythromycin improves transit

times and image quality in people undergoing capsule endoscopy, and trials of non-antibiotic derivatives of erythromycin (ABT-229), have also been excluded.

One relevant systematic review ([Maganti et al. 2003](#)) was identified, which contained most of the evidence in this summary. This review identified only crossover studies and uncontrolled trials, all of which enrolled fewer than 20 participants. Trials with fewer than 20 participants, or cohort studies and case series, would not usually meet the inclusion criteria. However, these trials were reviewed on the basis that they had been identified through a systematic review, which was a study design that met the criteria for inclusion in this evidence summary.

The search results were reviewed to identify whether any relevant randomised controlled trials of oral erythromycin for treating gastroparesis (of any underlying cause) in adults had been published after the systematic review, but no further trials were identified. Following on from this, in view of the limited evidence identified, a further search was performed to identify any relevant observational data published since the systematic review. A single study, a retrospective chart review ([Dhir and Richter 2004](#)) was identified.

## 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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