

# Acute diarrhoea in adults: racecadotril

## Evidence summary

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## Overview

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

## *Key points from the evidence*

Racecadotril received a UK marketing authorisation in September 2011 and was launched in the UK in October 2012. It has been licensed in parts of Europe for some time, for example in France for more than 20 years.

Racecadotril is licensed for the symptomatic treatment of acute diarrhoea in adults. It is also licensed for the complementary symptomatic treatment of acute diarrhoea in infants (aged over 3 months) and in children together with oral rehydration and the usual support measures, when these measures alone are insufficient to control the clinical condition. Use in children is the subject of a separate [evidence summary](#).

This evidence review is based on the 2 studies comparing racecadotril with loperamide for treating acute diarrhoea in adults. Both of these studies suggest that racecadotril and loperamide are similarly effective in reducing the duration of diarrhoea and the number of stools produced, and racecadotril has fewer adverse effects than loperamide, particularly constipation and abdominal distension. However, both studies have limitations affecting their validity and application to UK practice.

One of these 2 studies (Prado 2002; n=945) found that the mean duration of diarrhoea was 55 hours in both the racecadotril and loperamide groups (no significant difference). Significantly more patients in the loperamide group experienced constipation (25% compared with 16%, p=0.001). This study was undertaken in 14 countries outside Europe, where the aetiology and severity of diarrhoea is likely to differ from the UK, which limits its applicability to UK practice.

The second study (n=157) was undertaken in France by Vetel et al. (1999). It found that the mean number of stools passed until recovery and the mean duration of diarrhoea were similar with racecadotril and loperamide (3.5 compared with 2.9, and 14.9 hours compared with 13.7 hours respectively). The statistical significance of the difference between the groups was not given. The incidence of constipation was higher among patients treated with loperamide (18.7% compared with 9.8%) but this difference was not statistically significant.

Racecadotril appears to be well tolerated. The adverse effect most commonly reported is headache.

Local decision makers will need to consider the available evidence when making decisions about using racecadotril.

#### Key evidence

Prado D (2002) [A multinational comparison of racecadotril and loperamide in the treatment of acute watery diarrhoea in adults](#). *Scandinavian Journal of Gastroenterology* 37: 656–61

Vetel JM, Berard H, Fretault N et al. (1999) [Comparison of racecadotril and loperamide in adults with acute diarrhoea](#). *Alimentary Pharmacology and Therapeutics* 13 (Suppl. 6): S21–6

### *About this evidence summary*

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, but this summary is not NICE guidance.

### Relevance to NICE guidance programmes

Racecadotril was not considered appropriate for a NICE technology appraisal and is not currently planned into any other NICE work programme.

NICE has not published guidance on managing acute diarrhoea due to gastroenteritis in adults. [Diarrhoea and vomiting caused by gastroenteritis: diagnosis, assessment and management in children younger than 5 years](#) (NICE clinical guideline 84) was published in 2009. The Guideline Development Group reviewed 2 randomised placebo-controlled trials that looked at the effectiveness of racecadotril for treating diarrhoea in children. The Guideline Development Group concluded that, at that time, there was evidence that racecadotril had an antidiarrhoeal effect but further research was needed to examine the possible clinical and health economic benefits that might be associated with its use in the UK.

## Introduction

The [Health Protection Agency](#) defines acute diarrhoea as 3 or more episodes of partially formed or watery stool in a day, lasting for less than 14 days. Bacterial and viral infections account for most episodes of acute diarrhoea in adults. Viruses are the most common infectious cause in the community. Among people who consult their GP, *Campylobacter* species and rotavirus are the most common organisms isolated, although norovirus infections are increasing (see the Clinical Knowledge Summary on [diarrhoea – adults assessment](#)).

Gastrointestinal infection affects as many as 1 in 5 people in England each year, of whom 1 in 6 presents to a GP ([Wheeler et al. 1999](#)). According to the [Health Protection Agency](#), most infectious diarrhoea is self-limiting: nearly half of episodes last less than 1 day. In developed countries, dehydration secondary to gastroenteritis can lead to hospital admission, but death is uncommon. Older people are at greatest risk of death (see the Clinical Knowledge Summary on [gastroenteritis](#)).

Prevention or reversal of dehydration is the priority in acute diarrhoea and gastroenteritis, particularly in frail and older people. The [British national formulary](#) (BNF) advises that antimotility drugs may be used to relieve symptoms of uncomplicated acute diarrhoea in adults; it may also be necessary to use oral rehydration salt (ORS) solution.

[Faecal incontinence: the management of faecal incontinence in adults](#) (NICE clinical guideline 49) advises that antidiarrhoeal medication should be offered to people with faecal incontinence associated with loose stools once other causes (such as excessive laxative use, dietary factors and other medication) have been excluded.

The [BNF](#) advises that antispasmodics are occasionally of value in treating abdominal cramp associated with diarrhoea but they should not be used for primary treatment. Antibacterial drugs are generally unnecessary in simple gastroenteritis because the complaint usually resolves quickly

without them, and infective diarrhoeas in the UK often have a viral cause. Systemic bacterial infection does, however, need appropriate systemic treatment.

## Product overview

### *Drug action*

Racecadotril is an intestinal antisecretory enkephalinase inhibitor that inhibits the degradation of endogenous enkephalins. It thereby reduces the hypersecretion of water and electrolytes into the intestine. Unlike antimotility drugs, it does not modify the duration of intestinal transit (see the [summary of product characteristics](#)).

### *Licensed therapeutic indication*

Racecadotril received a UK marketing authorisation in September 2011 and was launched in the UK in October 2012. It has been licensed in parts of Europe for some time, for example in France for more than 20 years (Abbott Healthcare Products Limited: personal communication December 2012).

Racecadotril is licensed for the symptomatic treatment of acute diarrhoea in adults when causal treatment is not possible. If causal treatment is possible, racecadotril can be administered as a complementary treatment (see the [Hidrasec summary of product characteristics](#)).

Racecadotril is also licensed for the complementary symptomatic treatment of acute diarrhoea in infants (aged over 3 months) and in children together with oral rehydration and the usual support measures, when these measures alone are insufficient to control the clinical condition, and when causal treatment is not possible. If causal treatment is possible, racecadotril can be administered as a complementary treatment (see the summaries of product characteristics for [infants](#) and [children](#)). The evidence to support its use in children is discussed in a separate [evidence summary](#).

### *Course and cost*

One 100 mg capsule should be taken initially regardless of the time of day. Subsequently the dose is 1 capsule 3 times daily, preferably before main meals. Treatment should be continued until 2 normal stools are recorded and should not exceed 7 days (see the [summary of product characteristics](#)).

The current NHS cost of racecadotril 100 mg is £8.42 for a 20-capsule pack (excluding VAT; cost taken from [MIMS](#), February 2013).

## Evidence review

This evidence review is based on the 2 largest studies ([Prado 2002](#) and [Vetel et al. 1999](#)) comparing racecadotril with an active comparator for treating acute diarrhoea in adults. Although other published studies are available they were excluded because they included fewer patients (less than 70) or used placebo as a comparator.

### A multinational comparison of racecadotril and loperamide in the treatment of acute watery diarrhoea in adults ([Prado 2002](#))

- Design: single-blind, randomised controlled trial in 21 centres in 14 countries (Brazil, Cameroon, Costa Rica, Guatemala, Indonesia, the Ivory Coast, Kenya, Nigeria, Mexico, Morocco, Pakistan, the Philippines, Tunisia and Vietnam).
- Population: 945 outpatients aged 18 years or over (mean age 36 years, mean weight about 62 kg) with acute watery diarrhoea of presumed infectious origin, present for between 24 hours and 5 days, and at least 3 watery stools within the previous 24 hours (mean number of diarrhoeic stools in the previous 24 hours about 6.5; mean duration of diarrhoea 2.1 days).
- Intervention and comparison: patients were randomised to racecadotril 100 mg 3 times daily or loperamide 2 mg 3 times daily until diarrhoea resolved (12 hours without stools or 2 consecutive normal stools) or for a maximum of 7 days. Concomitant medication other than paracetamol and oral rehydration salt (ORS) solution was not permitted during the study.
- Outcomes: the primary outcome was duration of diarrhoea, defined as the time from the first dose of study drug to the appearance of the first formed stool. Secondary outcome measures included overall clinical response (clinical success or failure at 10–14 days) and occurrence and duration of abdominal pain and distension. The main safety outcomes were adverse events and occurrence of constipation (no stools for 36 hours or more).

**Table 1 Summary of the study:**[Prado \(2002\)](#)

	Racecadotril	Loperamide	Analysis <sup>a</sup>
Randomised	n=473	n=472	
Efficacy	n=473	n=471	

Primary outcome: duration of diarrhoea	Not stated	Not stated	<u>Hazard ratios</u> not stated. However, the authors report that the difference in recovery rates at 72 hours is in keeping with equivalence (less than +/-5% difference between the treatments)
Median duration of diarrhoea	55.0 hours (95% CI 50.0 to 65.0 hours)	55.0 hours (95% CI 48.0 to 66.0 hours)	Significance not given
Selected secondary outcomes:			
Overall clinical response	92%	93%	Significance not given
Median duration of abdominal pain	11 hours	10 hours	Significance not given
Median duration of abdominal distension	5.4 hours	24.4 hours	p=0.0001
<b>Safety</b>	n=473	n=472	
Any adverse event	14.2% (67/473)	23.9% (113/472)	p=0.001
Constipation	16% (74/473)	25% (116/472)	p=0.001

Abbreviations: CI, confidence interval.

<sup>a</sup> Initial identification of the intention to treat (ITT) to treat population excluded almost 25% of the treated population, largely because of missing data points. Missing data were replaced using unspecified predetermined criteria and a further analysis performed. It is this post-hoc analysis that is presented here, although the study authors state that the overall conclusion for both ITT analyses did not differ.

**Comparison of racecadotril and loperamide in adults with acute diarrhoea (Vetel et al. 1999)**

- Design: double-blind, randomised controlled trial in 34 general practices in France.
- Population: 157 outpatients aged 18 years or over (mean age 41 years) with acute diarrhoea, defined as at least 3 soft or liquid stools for between 24 hours and 5 days (mean number of diarrhoeic stools in the previous 24 hours 5.6; mean duration of diarrhoea about 40 hours).
- Intervention and comparison: patients were randomised to racecadotril (100 mg 3 times daily) or loperamide (4 mg initially then 2 mg after each diarrhoeic stool) until diarrhoea resolved (12 hours without stools or 2 consecutive normal stools) or for a maximum of 7 days. A double-placebo design was used in the study because the 2 drugs had different dosing regimens: patients randomised to racecadotril also received placebo capsules to take after each diarrhoeic stool and patients randomised to loperamide received placebo capsules to take 3 times a day. Paracetamol could be administered if the patient developed a fever but patients were withdrawn from the study if other concomitant medication was needed.
- Outcomes: the primary outcome measure was the number of diarrhoeic stools passed by the patient until recovery. Duration of diarrhoea and the change in associated symptoms and signs were also assessed. Safety outcomes included adverse events and the occurrence of constipation (no stools for at least 2 days).

**Table 2 Summary of the study: Vetel et al. (1999)**

	Racecadotril	Loperamide	Analysis <sup>a</sup>
Randomised	n=82	n=75	
Efficacy <sup>a</sup>	n=77 <sup>a</sup>	n=70 <sup>a</sup>	
Primary outcome: mean number of diarrhoeic stools passed until recovery +/- SEM	3.5+/-0.5	2.9+/-0.4	Significance not given
Selected secondary outcomes:			
Mean duration of diarrhoea +/- SEM	14.9+/-2.0 hours	13.7+/-2.2 hours	Significance not given
Safety	Number of patients not given		

Any adverse event	7.4%	12.0%	Significance not given
Constipation	9.8%	18.7%	No significant difference (p value not stated)
Abbreviations: SEM, standard error of the mean.			
<sup>a</sup> Vetel et al. state an <u>intention to treat</u> analysis was done. However, 5 patients from each group did not complete their evaluation sheets accurately and could not be evaluated for efficacy.			

## Clinical effectiveness

Prado (2002) found that racecadotril and loperamide were similarly effective: diarrhoea resolved in a median of 55 hours with both treatments. By days 10–14, 92% of patients taking racecadotril and 93% of patients taking loperamide had recovered.

The median duration of abdominal distension was significantly shorter with racecadotril compared with loperamide (5.4 hours compared with 24.4 hours,  $p=0.0001$ ) but the median duration of abdominal pain was similar in both treatment groups (11 hours compared with 10 hours respectively, significance not given).

Vetel et al. (1999) found that patients receiving racecadotril and loperamide passed a similar number of stools until their recovery from diarrhoea (mean 3.5 compared with 2.9, significance not given) and the mean duration of diarrhoea was similar in both treatment groups (14.9 hours compared with 13.7 hours respectively, significance not given).

## Safety

Prado (2002) found that significantly more patients in the loperamide group had an adverse event: 23.9% compared with 14.2% in the racecadotril group ( $p=0.001$ ). These were considered to be treatment related in 18% of patients taking loperamide and 9% of patients taking racecadotril (significance not given).

The most common treatment-related adverse events were constipation, abdominal distension, anorexia, headache and abdominal pain. Constipation was experienced by 16% of patients taking racecadotril and 25% of patients taking loperamide ( $p=0.001$ ) and was considered to be treatment related in 3.4% and 12.5% respectively (significance not given). Constipation and abdominal pain and distension are recognised adverse effects of loperamide.



[Vetel et al. \(1999\)](#) found that 7.4% of patients in the racecadotril group reported adverse events compared with 12.0% in the loperamide group (significance not given). More patients taking loperamide experienced constipation (18.7% compared with 9.8% of patients taking racecadotril). However, the difference was not found to be statistically significant. It is possible that this analysis may not have been sufficiently statistically powered to be able to detect a difference between the groups should one exist.

More than 37 million adults have been treated with racecadotril in Europe and overall exposure is more than 40 million adults worldwide (Abbott Healthcare Products Limited: personal communication January 2013). According to the summary of product characteristics, the adverse effect most commonly reported with racecadotril is headache (frequency of more than 1 in 100). Rash and erythema have been reported uncommonly (frequency of between 1 in 1000 and 1 in 100).

### *Evidence strengths and limitations*

These 2 studies suggest that racecadotril and loperamide are similarly effective in reducing the duration of diarrhoea and the number of stools produced, and racecadotril has fewer adverse effects than loperamide, particularly constipation. However, both studies have limitations affecting their validity and application to UK practice.

The larger study by [Prado \(2002\)](#) was undertaken in 14 countries where the aetiology and severity of diarrhoea is likely to differ from this country, limiting its applicability to UK practice. The mean duration of diarrhoea at study entry was 2 days (whereas according to the [Health Protection Agency](#) most infectious diarrhoea in the UK is self-limiting and nearly half of episodes last less than 1 day); only 14% of patients were reported by the study authors as 'Caucasian'; and the average weight of patients was only 62 kg.

The dosage of loperamide used in the Prado study (2 mg 3 times daily) did not reflect UK practice. The [BNF](#) recommends 4 mg initially followed by 2 mg after each diarrhoeic stool (usual dose 6–8 mg daily, maximum 16 mg daily). It is possible that loperamide might be more effective than racecadotril 100 mg 3 times a day at dosages greater than 6 mg daily. However, more adverse effects might be seen with higher dosages of loperamide.

Although the investigators responsible for the clinical evaluation of the patients were unaware which medication each patient received, patients were aware of the treatment (single-blinding) which may have introduced bias. In addition, the method of allocation was not described and it is

unclear whether allocation was concealed; unconcealed allocation is another potential source of bias.

The smaller study by Vetel et al. (1999) was conducted in France where the aetiology and severity of diarrhoea is likely to be similar to the UK. However, it has limitations which may affect its validity.

No measures of statistical significance or likely certainty, such as p values or confidence intervals, were given for the comparisons between racecadotril and loperamide. Therefore, it is difficult to estimate the true effects of racecadotril. The Vetel study was double blind but it is unclear whether allocation was concealed.

The mean ages of patients included in the 2 studies (Prado 2002 and Vetel et al. 1999) were 36 years and 41 years respectively. Therefore, the results may not be applicable to older people, the group of adults who are at greatest risk of dehydration and death from acute diarrhoea (see the Clinical Knowledge Summary on gastroenteritis). The incidence of severe dehydration or hospitalisation was not assessed in either study.

An additional small double-blind randomised controlled trial in nursing homes in Italy (Gallelli et al. 2010) compared racecadotril (100 mg 3 times daily) and loperamide (4 mg initially then 2 mg after each diarrhoeic stool, maximum 8 mg daily) in 61 older people (mean age 82 years) with acute diarrhoea and no signs of acute dehydration or bacterial infection. It found that racecadotril was statistically significantly more effective than loperamide. The duration of diarrhoea was 36 hours in the racecadotril group and 63 hours in the loperamide group ( $p < 0.01$ ). More patients in the loperamide group experienced adverse events (60% compared with 12%, significance not given); the most frequently reported adverse events were constipation and nausea.

The authors considered that the low efficacy of loperamide in this study could be related to drug interactions: all patients were taking potentially interacting drugs. The study was double blind but details of blinding of the 2 different dosage regimens are not given and it is not clear whether allocation was concealed. The study included only 61 patients. Small studies have limitations and need to be interpreted carefully because they do not normally yield reliable or precise estimates (Hackshaw 2008).

## Context

### Treatment alternatives

The [BNF](#) states that antimotility drugs may be used to relieve symptoms of uncomplicated acute diarrhoea in adults; it may also be necessary to use oral rehydration salt (ORS) solution.

### Costs of treatment alternatives

Drug	Usual dosage <sup>a</sup>	7-day cost excluding VAT
Racecadotril 100 mg <sup>b</sup>	1 capsule 3 times a day	£8.42 <sup>c</sup>
Loperamide 2 mg <sup>d</sup>	6 to 8 mg daily	Oral solution 1 mg/5 ml £2.46 to £3.28 <sup>e</sup> 2 mg capsules £0.66 to £0.88 <sup>e</sup> 2 mg tablets £1.51 to £2.01 <sup>e</sup> 2 mg oral lyophilisates (Instants) £5.86 to £7.81 <sup>e</sup>
Codeine phosphate <sup>d</sup>	30 mg 3 to 4 times daily	Oral solution 25 mg/5 ml £1.33 to £1.78 <sup>e</sup> 30 mg tablets £1.12 to £1.49 <sup>e</sup>
Co-phenotrope 2.5/ 0/025 mg tablets <sup>d</sup>	4 tablets, followed by 2 tablets every 6 hours until diarrhoea is controlled	£6.23 <sup>e</sup>
<p><sup>a</sup> The doses shown do not all represent the full range that can be used and they do not imply therapeutic equivalence.</p> <p><sup>b</sup> Dose taken from the <a href="#">Hidrasec summary of product characteristics</a>.</p> <p><sup>c</sup> Cost taken from <a href="#">MIMS</a> February 2013.</p> <p><sup>d</sup> Doses taken from the <a href="#">British national formulary</a>.</p> <p><sup>e</sup> Costs taken from <a href="#">Drug Tariff</a> February 2013.</p>		

In adults, ORS solution may be used alone as a treatment alternative to racecadotril and other antidiarrhoeal drugs, or it may be used with these drugs. It is difficult to give a 7-day cost because

the dosage of ORS solution is imprecise. According to fluid loss, 1 to 2 sachets are usually used after every loose motion. The cost of a 20-sachet pack is (excluding VAT; costs taken from [MIMS](#), February 2013):

- £6.72 for Dioralyte
- £7.13 for Dioralyte Relief
- £4.99 for Electrolade.

## Estimated impact for the NHS

### *Likely place in therapy*

Racecadotril is licensed for the symptomatic treatment of acute diarrhoea in adults when causal treatment is not possible. If causal treatment is possible, racecadotril can be administered as a complementary treatment (see the [Hidrasec summary of product characteristics](#)).

Although racecadotril appears to have similar efficacy to loperamide in reducing the duration of diarrhoea and frequency of stool output, and causes fewer adverse effects, it is unclear where it fits within current UK practice. According to the [Health Protection Agency](#) most infectious diarrhoea in the UK is self-limiting: nearly half of episodes last less than 1 day. Specialists have suggested that racecadotril might have a place in the treatment of travel-associated diarrhoea or chronic diarrhoea of unknown cause. However, evidence from clinical studies is needed before this can be recommended.

Assuming symptomatic treatment of diarrhoea is necessary, racecadotril is more expensive than antimotility agents, which are the current first-line option. The manufacturers of racecadotril suggest that the adults most likely to benefit are those with acute diarrhoea in which inhibition of peristalsis, abdominal distension or constipation should be avoided (Abbott Healthcare Products Limited: personal communication December 2012). However, further research is necessary to examine the possible clinical and health economic benefits that might be associated with use of racecadotril in the UK.

Local decision makers will need to consider the available evidence when making decisions about using racecadotril.

## *Estimated usage*

It is not possible to provide estimated usage based on the available data.

Between November 2011 and October 2012, more than 1.6 million items of loperamide capsules, tablets and orodispersible tablets were prescribed in primary care in England, at a cost of over £4.6 million. Over the same period, almost 548,000 items of ORS solution were prescribed at a cost of almost £2.7 million (NHS Business Services Authority: personal communication January 2013).

## References

Abbott Healthcare Products Limited (2012) [Hidrased infant 10 mg granules for oral suspension summary of product characteristics](#) [online; accessed 18 February 2013]

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For information about the process used to develop this evidence summary, see [Evidence summaries: new medicines – interim process statement](#).

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## Contact NICE

National Institute for Health and Clinical Excellence  
Level 1A, City Tower, Piccadilly Plaza, Manchester M1 4BT

[www.nice.org.uk](http://www.nice.org.uk); [nice@nice.org.uk](mailto:nice@nice.org.uk); 0845 033 7780