

## Evidence Review for Prescribing Clinical Network

**Treatment: Racecadotril (Hidrasec®) for the symptomatic treatment of acute diarrhoea in adults and children over three months**

**Prepared by: Clare Curran**

**Topic Submitted by: Clare Curran**

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*Medicines Management Team, Cedar Court, Guildford Road, Leatherhead, KT229AE  
Telephone: 01372 201700 Email: [ThePAD@nhs.net](mailto:ThePAD@nhs.net)*

### **Summary page**

**How strong is the evidence for claimed efficacy?** Grade A – 2 RCT (but both RCTs have limitations affecting their validity and relevance to UK practice – see 3.4).

**Potential advantages in terms of: efficacy, compliance, pharmacokinetics, drug interactions and adverse effects?** No evidence to suggest racecadotril is more effective than the established antidiarrhoeal agent, loperamide. Fewer reports of adverse effects (rebound constipation and abdominal distension) than with loperamide (but both RCTs have limitations affecting their validity and relevance to UK practice – see 3.4).

**Is there a clear place in therapy / treatment pathway?** No

**Is monitoring for efficacy required?** Yes – symptom control

**Is monitoring for toxicity required?** No

**Is dose titration required?** No

**Traffic light status / Role of GP:** Black status proposed

**Role of the specialist:** Not applicable

### **Financial implications:**

Adults: The cost of racecadotril is higher than for any of the alternative treatments available for adults.

Children over three months: The cost of racecadotril would be in addition to the cost of oral rehydration therapy.

It is estimated that if 50% of patients per year are prescribed racecadotril instead of loperamide, the increase in prescribing cost would be approximately £11,000 per 100,000 of population. There is a lack of evidence to show the use of racecadotril would decrease hospital admissions, reduce hospital stays or improve recovery rate.

**National Guidance available:**

- Racecadotril was not considered appropriate for a NICE technology appraisal and is not currently planned into any other NICE work programme.
- The NICE Guideline Development Group reviewed two randomised placebo-controlled trials for the effectiveness of racecadotril for treating diarrhoea in children. It concluded racecadotril had an antidiarrhoeal effect but that further studies were needed to determine the possible clinical and health economic benefits.
- The Scottish Medicines Consortium does not recommend the use of racecadotril in NHS Scotland for the treatment of acute diarrhoea in children or adults.
- The All Wales Medicines Strategy Group does not endorse the use of racecadotril for the treatment of acute diarrhoea in children or adults.

**Recommendation for PCN:**

**Racecadotril is not routinely recommended for prescribing in primary care (black status). There is a lack of good clinical evidence that it offers benefit over existing treatments and it is less cost effective.**

## **1. Purpose of the Review**

To review the evidence for the use of racecadotril (Hidrasec®), as an adjunct to rehydration, for the symptomatic treatment of uncomplicated acute diarrhoea in adults and children over three months.

## **2. Appropriateness**

### **2.1 The patient:**

Racecadotril is licensed for use in adults and children over three months:

Adults: racecadotril is indicated for the symptomatic treatment of acute diarrhoea in adults when causal treatment is not possible.<sup>1</sup>

Children over 3 months of age: racecadotril is indicated for the symptomatic treatment of acute diarrhoea in infants (older than 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.<sup>2</sup>

### **2.2 The problem:**

#### **Definition:**

There is no universally agreed definition for diarrhoea. The British Society of Gastroenterology defines diarrhoea in adults as the abnormal passage of loose or liquid stools more than three times daily and/or a volume of stool greater than 200 g/day. There is no consensus on the duration of symptoms that define chronic as opposed to acute diarrhoea. It is generally accepted that symptoms persisting for longer than four weeks would be considered chronic and would require further investigation.<sup>3</sup>

#### **Effects and prognosis:**

Symptoms of acute diarrhoea are often short-term and resolved within days. The main risk is dehydration. The priority in managing acute diarrhoea is the prevention or reversal of fluid and electrolyte depletion. This is especially important for certain groups of patients including infants and the frail and elderly.

#### **Etiology:**

There are a number of possible causes of acute diarrhoea including viral infection, food poisoning, contaminated water, food intolerance, anxiety and the adverse effects of certain medicines.

#### **Diagnosis:**

Diagnosis is generally based on symptoms. In some cases a stool sample may be required to identify the cause of suspected infection: for example if the patient is particularly unwell, has blood in their stools, food poisoning is suspected, there has been recent overseas travel, or their symptoms are persisting.

### **2.3 The Intervention:**

Racecadotril has an antisecretory action as it decreases the intestinal hypersecretion of water and electrolytes induced by the cholera toxin or inflammation. It does not have effects on basal secretory activity. Racecadotril exerts antidiarrhoeal action, without modifying the duration of intestinal transit.<sup>1</sup>

#### **How does it work:**

Racecadotril is a pro-drug of thiorphan, an enkephalinase inhibitor. By protecting enkephalins from enzymatic degradation, their action is prolonged. Thus the inhibition of the breakdown of endogenous opioids reduces the hypersecretions in the small intestine that are characteristic of diarrhoea.<sup>1</sup> It works locally by reducing the volume of diarrhoea rather than by decreasing gastro-intestinal transit time.

#### **Care setting:**

The Marketing Authorisation does not restrict prescribing to specialists; could be prescribed in primary or secondary care.

#### **Frequency:**

The dose is given three times a day via the oral route and should be continued until two normal stools are recorded. The maximum duration of treatment is seven days. Long-term treatment with racecadotril is not recommended.<sup>1</sup>

Three presentations of racecadotril are available: 10mg granules for oral suspension (infants over three months weighing less than 13kg), 30mg granules for oral suspension (children weighing 13kg or more) and 100mg capsules (adults). Dosage for infants and children is based on body weight.

### **2.4 Alternative treatments:**

The priority in managing diarrhoea is to prevent or treat fluid and electrolyte depletion. Replacement of fluid and electrolytes lost through diarrhoea can be achieved by the use of oral rehydration therapy.

Adults: antimotility drugs, such as loperamide, codeine and co-phenotrope, are used in the management of uncomplicated acute diarrhoea; with attention to fluid replacement if appropriate.

Children: antidiarrhoeals are not recommended for acute diarrhoea for children under the age of five years.<sup>4</sup> Some antimotility agents such as loperamide syrup and co-phenotrope tablets are licensed in children aged 4 years and over, but the BNF for Children advises that they are not recommended for use in children under 12 years.

Antibiotics should not be given routinely for the treatment of acute diarrhoea.

### **3. Effectiveness**

#### **3.1 Expected benefits**

To manage symptoms and improve the recovery rate of acute diarrhoea by reducing intestinal hypersecretions.

#### **3.2 Is there a plausible biological basis for effectiveness?**

Yes

#### **3.3 Side-effects/complications**

- Undesirable effects in children and infants: tonsillitis, rash, erythema (uncommon:  $\geq 1/1,000$  to  $< 1/100$ ).<sup>2</sup>
- Undesirable effects in adults: headache (common  $\geq 1/100$  to  $< 1/10$ ), rash, erythema. (uncommon:  $\geq 1/1,000$  to  $< 1/100$ ).<sup>1</sup>
- Racecadotril has no or negligible influence on the ability to drive and use machines.
- Hepatic and renal impairment: use with caution in adults; avoid in children.
- Pregnancy and breast-feeding: avoid (no information available).
- To date, no interactions with other medicinal products have been described in humans.

#### **3.4 Review of evidence**

Racecadotril was launched in the UK in October 2012. However it has been available in other parts of the Europe for some time. It has been licensed in France for more than 20 years. Despite this there is a lack of robust studies comparing racecadotril with other antidiarrhoeal agents.

#### **Use of racecadotril in children**

- NICE(Clinical Guideline 84) recommends that for diarrhoea caused by gastroenteritis in children under 5 years of age, the treatment of dehydration using oral rehydration preparations should be a priority and that antidiarrhoeals should not be given.<sup>4</sup>
- The NICE Guideline Development Group reviewed two randomised placebo-controlled trials that looked into the effectiveness of racecadotril for treating acute diarrhoea in children. It concluded there was evidence racecadotril had an antidiarrhoeal effect but noted recommended research was needed to determine any possible clinical and health economic benefits.
- The BNF for Children does not recommend the use of antimotility drugs in children under 12 years with acute diarrhoea.
- The Scottish Medicines Consortium (SMC) does not recommend the use of racecadotril in NHS Scotland for the treatment of acute diarrhoea in children due to insufficient evidence that it improves the recovery rate.<sup>5</sup>
- Racecadotril is not recommended for use within NHS Wales for the complementary symptomatic treatment of acute diarrhoea in infants (older than 3 months) and children. The All Wales Medicines Strategy Group (AWMSG) was not convinced that the case presented for clinical and cost effectiveness supported the use of this medicine in NHS Wales.<sup>6</sup>
- The most recent World Health Organisation (WHO) Model List of Essential Medicines for Children (intended for use in children up to 12 years of age) was

published in 2011 and did not include racecadotril. WHO recommended treatments for diarrhoea are oral rehydration preparations and zinc sulphate (due to the prevalence of zinc deficiency in malnourished children).<sup>7</sup>

#### Use of racecadotril in adults

- NICE has not published guidance on the managing acute diarrhoea caused by gastroenteritis in adults. It is common practice to relieve symptoms using antimotility drugs (sometimes self-administered) and to use oral rehydration preparations as necessary.
- There was no case concerning the use of racecadotril in adults submitted by the marketing authorisation holder to the Scottish Medicines Consortium. The SMC consequently does not endorse its use in adults.<sup>5</sup>
- In the absence of a submission from the holder of the marketing authorisation, racecadotril capsules are not endorsed for use within NHS Wales by the All Wales Medicines Strategy Group (AWMSG) for the symptomatic treatment of acute diarrhoea in adults.<sup>6</sup>
- A recent NICE Evidence Summary<sup>8</sup> considered two studies comparing racecadotril and loperamide for treating acute diarrhoea in adults (one single-blind randomised controlled trial, one double-blind randomised controlled trial). Other published studies were excluded due to low patient numbers or placebo being used as the comparator. Both studies concluded that racecadotril and loperamide have similar efficacy in reducing the duration of diarrhoea and the number of stools produced. There were fewer reports of rebound constipation and abdominal distension with racecadotril than with loperamide. However these studies have limited application to UK practice. One study (n=945) took place in 14 non-European countries thus limiting its application to UK practice since the severity and cause of the diarrhoea is likely to differ from the UK. Comparison was with a dose of loperamide that does not reflect UK prescribing (lower dose). The other study took place in France (n=157) but was on a small scale and failed to give the statistical significance of changes to the duration of diarrhoea and the number of stools produced.

### **4. Summary of Key Points for Consideration**

#### **4.1 National guidance:**

- NICE recommends that for diarrhoea caused by gastroenteritis in children under 5 years of age, the treatment of dehydration should be a priority and that antidiarrhoeals should not be given.<sup>4</sup>
- The Scottish Medicines Consortium does not recommend the use of racecadotril in NHS Scotland for the treatment of acute diarrhoea in children or adults.<sup>5</sup>
- The All Wales Medicines Strategy Group (AWMSG) does not recommend the use of racecadotril in NHS Wales for the treatment of acute diarrhoea in children or adults.<sup>6</sup>
- The World Health Organisation (WHO) Model List of Essential Medicines for Children (intended for use for children up to 12 years of age) does not include racecadotril. The only recommended treatments for diarrhoea are oral rehydration salts and zinc sulphate, (due to the prevalence of zinc deficiency in malnourished children).<sup>7</sup>

## 4.2 Efficacy

Whilst two studies have found that loperamide and racecadotril have similar efficacy, their design and the data obtained are not considered robust. There is no evidence to suggest racecadotril is more effective than the established antidiarrhoeal agent, loperamide.

## 4.3 Potential Benefits over existing therapy

Two studies reported less rebound constipation and abdominal distension with racecadotril than with loperamide.

## 4.4 Potential disadvantages

Fluid and electrolyte depletion may not be adequately treated in children. Parents or carers may not fully appreciate that oral rehydration therapy is the priority in children and that this should accompany the use of racecadotril. Racecadotril is indicated for the symptomatic treatment of acute diarrhoea in infants (older than 3 months) and in children together with oral rehydration and the usual support measures.

## 4.5 Budgetary Impact

### 4.5.1 Cost:

Adults:

Drug	Dose <sup>9</sup>	Cost for 7 days <sup>10</sup>
Racecadotril capsules 100mg	100mg three times daily	£8.42
Loperamide capsules 2mg	6-8mg daily (usual dose) 16mg daily (max dose)	£1.07 - £1.43
Codeine phosphate tablets 30mg	30mg 3-4 times daily	£1.06 - £1.41
Co-phenotrope tablets 2.5mg/25micrograms	Initially four tables, followed by two tablets every six hours	£6.23

Children over three months of age:

Less than 9kg taking one 10mg sachet three times daily: £8.42

Between 9kg and 13kg taking two 10mg sachets three times a day: £16.84

Between 13kg and 27kg taking one 30mg sachet three times daily: £8.42

Over 27kg taking two 30mg sachets three times daily: £16.84

(No cost comparison made with other antidiarrhoeals since alternative products are not recommended for use in children)

Between November 2011 and October 2012 there were 1.6 million prescriptions for loperamide in England. This equates to around 3,200 prescriptions per 100,000 population for loperamide.<sup>11</sup> It is estimated that if 50% of these patients (1,600) per year are prescribed racecadotril instead of loperamide, this would increase prescribing costs by around £11,000 per 100,000 population.

### 4.5.2 Precedent setting:

NHS Scotland and NHS Wales do not recommend the use of racecadotril for the treatment of acute diarrhoea in adults and children over three months

Bedfordshire and Luton Joint Prescribing Committee does not recommend the use of racecadotril (April 2013).

Hull Clinical Commissioning Group does not recommend racecadotril for the treatment of acute diarrhoea (February 2013).

## **5. Conclusions and Recommendations**

There is a lack of robust evidence for racecadotril being more effective than other available antidiarrhoeal treatments. More studies are needed to confirm reports of fewer adverse effects with racecadotril than with loperamide. NICE guidance recommends that, in children under 5 years, the treatment of dehydration should be a priority and that antidiarrhoeals should not be given.

### **Recommendation for PCN:**

**Racecadotril is not routinely recommended for prescribing in primary care (black status). There is a lack of good clinical evidence that it offers benefit over existing treatments and it is less cost effective.**



## Appendix 1: Evidence search

Search terms used:

Resource	Used in this review?
<p>National Library for Health (NHL)  <a href="http://www.library.nhs.uk/Default.aspx">http://www.library.nhs.uk/Default.aspx</a></p> <p>A gateway site with access to other resources such as Reviews (Bandolier, Cochrane, CRD etc), Guidelines (e.g. NICE), Clinical Knowledge Summaries (CKS) and Journals including AMED, British Nursing Index, CINAHL, E-books, EMBASE, HMIC, MEDLINE, My Journals, PsycINFO, PubMed, Databases from Dialog.</p>	✓
<p>National Institute of Health and Clinical Excellence (NICE)  <a href="http://www.nice.org.uk/">http://www.nice.org.uk/</a></p> <p>NICE produces national guidance in three areas of health:</p> <ol style="list-style-type: none"> <li>1. Public health - guidance on the promotion of good health and the prevention of ill health</li> <li>2. Health technologies - guidance on the use of new and existing medicines, treatments and procedures within the NHS</li> <li>3. Clinical practice - guidance on the appropriate treatment and care of people with specific diseases and conditions within the NHS.</li> </ol>	✓ (through NHL)
<p>Bandolier  <a href="http://www.medicine.ox.ac.uk/bandolier/index.html">http://www.medicine.ox.ac.uk/bandolier/index.html</a></p> <p>Bandolier is a website about the use of evidence in health, healthcare, and medicine. Information comes from systematic reviews, meta-analyses, randomised trials, and from high quality observational studies.</p>	✓ (through NHL)
<p>Centre for Reviews and Dissemination  <a href="http://www.york.ac.uk/inst/crd/">http://www.york.ac.uk/inst/crd/</a></p> <p>CRD undertakes high quality systematic reviews that evaluate the effects of health and social care interventions and the delivery and organisation of health care. Databases maintained by CRD include Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA) Database</p>	✓ (through NHL)
<p>Scottish Intercollegiate Guidelines Network (SIGN)  <a href="http://www.sign.ac.uk/">http://www.sign.ac.uk/</a></p> <p>Scottish equivalent of NICE</p>	✓
<p>Medical Services Advisory Committee (Australia)  <a href="http://www.msac.gov.au/internet/msac/publishing.nsf/Content/home-1">http://www.msac.gov.au/internet/msac/publishing.nsf/Content/home-1</a></p> <p>The principal role of the Medical Services Advisory Committee (MSAC) is to advise the Australian Minister for Health and Ageing on evidence relating to the safety, effectiveness and cost-effectiveness of new medical technologies and procedures.</p>	✓

<p>Canadian Agency for Drugs and Technologies in Health (CADTH)  <a href="http://www.cadth.ca/index.php/en/home">http://www.cadth.ca/index.php/en/home</a>  The Canadian Agency for Drugs and Technologies in Health (CADTH) is a national body that provides Canada’s federal, provincial and territorial health care decision makers with credible, impartial advice and evidence-based information about the effectiveness and efficiency of drugs and other health technologies.</p>	✓
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## Appendix 2: Grading of evidence

- lb: at least one randomised controlled trial

## Appendix 3: References

1. Summary of Product Characteristics (last updated 10/09/2013)  
<http://www.medicines.org.uk/emc/medicine/27107/SPC/Hidrasec+100mg+Hard+capsules/>
2. Summary of Product Characteristics (last updated 11/9/2013)  
<http://www.medicines.org.uk/emc/medicine/27108/SPC/Hidrasec+children+30mg+granules+for+oral+suspension/>
3. Guidelines for the investigation of chronic diarrhoea, 2<sup>nd</sup> edition. *Gut* 2003;52(Suppl V):v1–v15. Thomas PD et al. [http://www.bsg.org.uk/pdf\\_word\\_docs/cd\\_body.pdf](http://www.bsg.org.uk/pdf_word_docs/cd_body.pdf)
4. NICE Clinical Guideline 84: Diarrhoea and vomiting in children, April 2009.  
<http://www.nice.org.uk/nicemedia/live/11846/43843/43843.pdf>
5. Scottish Medicines Consortium: Racecadotril 10mg, 30mg granules for oral suspension SMC No. (818/12). 9 November 2012.  
[http://www.scottishmedicines.org.uk/files/advice/racecadotril\\_Hidrasec\\_FINAL\\_November\\_2012\\_for\\_website.pdf](http://www.scottishmedicines.org.uk/files/advice/racecadotril_Hidrasec_FINAL_November_2012_for_website.pdf)
6. All Wales Medicines Strategy Group: Racecadotril Reference No. 1545 Appraisal information. 25 April 2012.  
<http://www.awmsg.org/awmsgonline/app/appraisalinfo/1545>
7. 4th World Health Organisation Model List of Essential Medicines for Children (April 2013). <http://www.who.int/medicines/publications/essentialmedicines/en/index.html/>
8. NICE Evidence Summary New Medicine ESNM11: Acute diarrhoea in adults: racecadotril 12 March 2013.  
<http://publications.nice.org.uk/esnm11-acute-diarrhoea-in-adults-racecadotril-esnm11/relevance-to-nice-guidance-programmes>
9. BNF 66 (September 2013). BMJ Group and RPS Publishing.
10. Drug Tariff (February 2014) <http://www.nhsbsa.nhs.uk/924.aspx>
11. Bedfordshire and Luton Joint Prescribing Committee. Bulletin 180: Racecadotril for the symptomatic treatment of acute diarrhoea in adults and children over 3 months (April 2013).