JPC Recommendation:
The use of racecadotril is not recommended.

New Medicine Review

Racecadotril for the symptomatic treatment of acute diarrhoea
(adults and children over 3 months)

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Racecadotril (Hidrasec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Document status</td>
<td>Final bulletin approved by the Bedfordshire and Luton Joint Prescribing Committee, 24th April 2013.</td>
</tr>
<tr>
<td>Date of last revision</td>
<td>24th April 2013</td>
</tr>
<tr>
<td>Proposed Sector of prescribing</td>
<td>Primary and Secondary care</td>
</tr>
</tbody>
</table>

Introduction

Racecadotril is a recently licensed treatment for the symptomatic treatment of acute diarrhoea in adults and children aged over 3 months although it has been in clinical use in France for over 20 years. Racecadotril offers an alternative to anti-motility agents such as loperamide, codeine or co-phenotrope. It works locally by decreasing the volume of diarrhoea rather than decreasing GI transit time and therefore in theory at least may be less likely to be associated with rebound constipation.

There is no national guidance on the management of acute diarrhoea in adults but NICE nor the BNFC do not support the use of anti-motility agents in children aged under 12 years but advocate the use of oral replacement salts.

In adults there are 4 published non-inferiority RCTs comparing it loperamide and overall it was shown to be similarly effective. None of the trials could be described as high quality in that key methodological detail is not provided. In one trial it was shown that racecadotril was less likely to be associated with...
Rebound constipation (NNT ~ 10 to prevent one additional case)

In children there is a meta-analysis of 9 placebo-controlled trials which show that compared with placebo (or used in addition to normal supportive care) it is associated with a reduction in the likelihood of still having diarrhoeal symptoms 48 hours after starting treatment (NNT ~ 4, to produce one additional responder at 48 hours). There is one RCT comparing it with loperamide which showed there to be no statistically significant difference between the treatments in terms of response rates.

Overall, racecadotril appears to be well tolerated.

It costs £8.42 to treat an adult with a 7-day course of racecadotril and between £8.42 and £16.84 to treat a child.

<table>
<thead>
<tr>
<th>The intervention Mechanism of action</th>
<th>Racecadotril decreases intestinal hypersecretion of water and electrolytes induced by cholera toxin or inflammation, exerting a rapid antidiarrhoeal action, without modifying the duration of intestinal transit.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Licensed indication</td>
<td>Racecadotril is indicated for the symptomatic treatment of acute diarrhoea in adults when causal treatment is not possible. If causal treatment is possible, then it can be administered as a complementary treatment. It is also licensed in infants (over 3 months old) and children as complementary symptomatic treatment of acute diarrhoea 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 [1].</td>
</tr>
<tr>
<td>Usual dosage</td>
<td>To initiate therapy in adults, one capsule (containing 100mg of racecadotril) is taken regardless of the time of day; after that, one capsule is taken three times daily preferably before the main meals [1]. Racecadotril is also available in 10mg sachets as granules for oral suspensions and is intended for children less than 13kg in weight and in 30mg sachets for children more than that. The recommended dose is determined according to body weight: 1.5 mg/kg per dose (corresponding to 1 to 2 sachets), three times daily at regular intervals. For both adults and children, treatment should be continued until two normal stools are recorded. Treatment should not exceed 7 days and long-term treatment with the drug is not recommended.</td>
</tr>
<tr>
<td>Treatment alternatives/ place in therapy</td>
<td>Possible active treatment alternatives are loperamide, codeine or co-phenotrope. Supportive therapies such as use of oral rehydration salts are encouraged.</td>
</tr>
<tr>
<td>Future alternatives</td>
<td>None apparent at present</td>
</tr>
<tr>
<td>National guidance</td>
<td>There is no national guidance in place for adults but it is common practice to support the use of anti-motility drugs (including self-medication) to relieve the symptoms of uncomplicated acute diarrhoea in adults and to recommend the use of oral rehydration salts (ORS) as necessary. In children aged under 5 years NICE do not recommend the use of antidiarrhoeal drugs but advocate the use of ORS for children with dehydration and those at risk of developing dehydration [2]. THE BNF for Children does not recommend the use of antimotility drugs in children with acute diarrhoea under 12 years [3]. The SMC do not support the use of racecadotril in children as they concluded that the manufacturer did not present a sufficiently robust economic or clinical case.[4] The manufacturer did not submit a case concerning use in adults and therefore the SMC cannot endorse use in this population either..</td>
</tr>
</tbody>
</table>
There are 7 RCTs of racecadotril adults with acute diarrhoea. Three of these compare with drug with placebo and four with loperamide. The 3 placebo-controlled studies are not addressed further in this section.

In a trial by Vettel et al, a total of 157 adult patients were randomised to either racecadotril or 4mg loperamide given initially then one 2mg capsule was taken after every loose stool [5]. The primary outcome was number of diarrhoeic stool passed until recovery (defined as the production of two consecutive normal stools or lack of stool for 12 hours). In intention to treat analysis, both groups of patients passed similar numbers of stool before recovery (3.5 +/- 0.5 for racecadotril vs. 2.9 +/- 0.4 for loperamide) although the statistical significance of this difference is not reported. Similarly the mean duration of diarrhoea was reported as being 14.9 hours vs. 13.7 hours respectively. In this trial it was also observed that racecadotril was associated with a lower incidence of adverse events (7.4% vs. 12%) and a lower incidence of rebound constipation (9.8% vs. 18.7%) – although this difference was not statistically significant the trial was not powered appropriately to assess this outcome.

In a trial by Prado et al, a total of 945 patients were randomised to either racecadotril or loperamide 2mg three times daily [6]. The primary outcome measure was duration of diarrhoea (defined as time from first dose of study medication to appearance of first formed stool). Only paracetamol and ORS were permitted to be taken concomitantly. The trial was not adequately powered. Analysis was performed by both ITT and per protocol (PP) population. Duration of diarrhoea in both treatment groups was similar: median duration was 55.0 hours (95% CI 50.0-65.0) for racecadotril and 55.0 hours (95% CI 48.0-66.0) for loperamide in the ITT population, and 48.0 hours (95% CI 47.0-51.0) for racecadotril and 48.0 (95% CI 46.0-49.0) in the PP population. In this trial it is reported that 14.2% of patients that received racecadotril and 23.9% of patients that received loperamide reported an adverse event, but racecadotril was associated with a significant reduction in the median duration of abdominal distension (5.4 hours vs. 24.4 hours, p = 0.0001).

In a small trial by Wang et al, 62 patients were randomised to either racecadotril or 2mg loperamide twice daily for a maximum of 7 days [7]. The primary outcome measure was duration of diarrhoea (defined as time from first dose of study medication to two consecutive formed stool or 12 hours with no stool). No additional anti-diarrhoeal medicines or concomitant therapies were permitted during the trial. All 62 patients were included in the ITT analysis and 48 in the PP analysis. In the ITT population, the mean duration of diarrhoea was 19.5 hours in the racecadotril group compared with 13.0 hours in the loperamide group (P=0.23), and in the PP population the mean duration of diarrhoea was 19.5 hours in the racecadotril group compared with 13.0 hours in the loperamide group (P=0.37). Both drugs were reported as well tolerated, although the lower rate of constipation reported in the racecadotril group compared with the loperamide group (12.9% for racecadotril vs., 29% for loperamide) was not statistically significant. This trial might also be criticised for the fact that the comparator might be viewed as sub-optimal loperamide regimen.

In a randomised double-blind trial of racecadotril and loperamide in the elderly...
nursing home population, a total of 61 patients with acute diarrhoea (defined as three or more liquid stools in 24 hours) without signs of severe dehydration were randomised to either racecadotril 100mg three times daily or 4mg loperamide initially then 2mg twice daily for a maximum of 4 days (8). The primary efficacy criterion was duration of diarrhoea in days from first treatment to recovery (defined as time from first dose of study medication to two consecutive formed stool or 12 hours with no stool). All 61 patients were included in the ITT analysis and 54 in the PP analysis. Patients in the racecadotril group had experienced 3.93 episodes (range 1-11) of diarrhoea before being randomised to treatment compared to 7.29 (range 2-16) in the loperamide group. The authors reported that normal stools were collected 36 +/- 4 hours in the racecadotril group compared with 63 +/- 6 hours in the loperamide group (p<0.01), but did not publish the data in the paper, so no further comment can be made regarding the results. Also, as above, this study could be criticised for using a sub-optimal dose of loperamide as comparator.

Use in children

There have been two systematic reviews published of the use of racecadotril compared with placebo in children. The first of these is not discussed further since the three trials it assesses are also incorporated into the larger, more recent analysis. There has also been a randomised controlled trial comparing racecadotril with loperamide.

The more recent systematic review included nine trials involving a total of 1,384 children (9). The children received either racecadotril or placebo. The age of children ranged from 1-71 months-two trials involved children under 3 months of age, the licensed age for receiving the drug. Four trials involved inpatient settings and five trials involved outpatient settings. It is reported that overall 50.3% of patients that received racecadotril were classified as responders compared with 25.8% of patients that received loperamide (p-value not stated, but this difference roughly equates to an NNT of 4). In this analysis a responder was defined as a patient with diarrhoea for less than 48 hours after adjusting for baseline dehydration and rotavirus. For inpatient studies, the ratio of mean stool output comparing racecadotril to placebo was 0.59 (95% CI 0.51-0.74, p<0.001) and for outpatient studies, the ratio of the mean number of diarrhoeic stools comparing racecadotril to placebo was 0.63 (95% CI 0.51 – 0.74, p<0.001).

In this analysis it is reported that 11.6% of children experienced an adverse event with racecadotril compared with 10.1% of those that received placebo.

A randomised trial has also compared the use of racecadotril and loperamide in children (10). A total of 102 children aged 2-10 years were randomised to either racecadotril (1.5mg/kg) or loperamide (0.03mg/kg) three times daily until recovery (defined as either the production of two normal stools, production of one normal stool followed by 12 hours no stool or no stool for 12 hours). The primary outcome was the number of diarrhoeic stools until recovery. Treatment with ORS, analgesics and anti-emetics was permitted, but treatment with aspirin, anti-diarrhoeal or anti-tussive medication was not. Patients who received racecadotril passed a mean of 2.7 +/- 0.4 stools before recovery compared with patients who received loperamide passing a mean of 2.1 +/- 0.4 stools. The differences were not statistically significant.

Safety

The SPC states that from the clinical trials [1]. Common unwanted effects (occurring in between 1 in 10 and 1 in 100 patients) were headache. Uncommon unwanted effects (occurring in between 1 in 100 and 1 in 1,000 patients) were rash and erythema (and also tonsillitis in those taking granules). Other unwanted effects were erythema multiforme, tongue oedema, face oedema, lip oedema, eyelid
oedema, angioedema, urticaria, erythema nodosum, rash papular, prurigo, pruritus and toxic skin eruption; the frequency of these other unwanted effects is unknown as it cannot be estimated from available data.

### Costs for adults

**Adults**

Racemadotril costs £8.42 for a 7-day course of 1 capsule 3x daily.

**Children**

Cost of 7-day course

- Less than 9kg taking 1x10mg sachet three times daily: £8.42
- Between 9 and 13kg taking 2x10mg sachets three times daily: £16.84
- Between 13 and 27kg taking 1x30mg sachet three times daily: £8.42
- Over 27kg taking 2x 30mg sachets three times daily: £16.84

### Costs of alternatives

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Cost for 7 day course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loperamide caps</td>
<td>6 to 8mg daily</td>
<td>£1.51 to £2.01</td>
</tr>
<tr>
<td>Codeine tabs</td>
<td>30mg 3-4/ day</td>
<td>£1.12 to £1.49</td>
</tr>
<tr>
<td>Co-phenotrope</td>
<td>1 - every 6 hours</td>
<td>£6.23</td>
</tr>
</tbody>
</table>

These agents are only licensed for use in children aged over 12 years and as such the dosage regimens are very similar to those described for adults. The cost described however would increase if liquid formulations were prescribed.

### Cost effectiveness (if available)

In the SMC analysis of the cost-effectiveness in children the manufacturer submitted a case in which it was estimated that administration of racemadotril would reduce overall treatment costs by £889 per 100 children treated and produce a QALY gain of 0.0067 per 100 children (or 34.5 quality adjusted minutes per child treated). This estimate of cost saving was primarily driven by a claim that use would lead to a 5% drop in the need to reconsult the GP and a 1% drop in subsequent hospital referrals. The SMC did not feel that this economic model was sufficiently robust in terms of the assumptions made.

### Potential number of patients in Bedfordshire and Luton Impact per 100,000 population

It is reported that between Nov 2011 and Oct 2012 there were over 1.6 million prescriptions for loperamide in England and 548,000 prescriptions for ORS – this equates to around 3200 and 1100 prescriptions per 100,000 population respectively. If we assume that 1500 people per year are prescribed a course of racemadotril instead of loperamide, this would increase prescribing costs by around £10,000 per 100,000 population.

### Affordability considerations

### Number Needed to Treat (NNT)

**Adults** – there is no evidence that racemadotril is more effective than loperamide; the evidence that does exist suggests they are comparable. However there is
**Number Needed to Harm (NNH)**

weak evidence that for every 10 patients treated with racecadotril instead of loperamide one less patient may experience rebound constipation.

**Children** – there is no evidence that racecadotril is more effective than loperamide but there is evidence that for every 4 patients given racecadotril in addition to normal supportive measures instead of just supportive measures alone one more patient will be diarrhoea-free at 48 hours.

<table>
<thead>
<tr>
<th>Ethics Equity</th>
<th>See attached assessment against ethical and commissioning principles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implementation</td>
<td>See attached assessment against ethical and commissioning principles</td>
</tr>
<tr>
<td>Patient choice/access considerations</td>
<td>See attached assessment against ethical and commissioning principles</td>
</tr>
</tbody>
</table>
### Decisions from other bodies

SMC – no in children as felt that clinical or economic case were not robust and not recommended in adults because the manufacturer did not make a submission.

Not applicable- published meta-analyses and RCTs in peer reviewed journals

### Grey literature Comments sought from –

### Points for consideration

Racecadotril is a competitor to loperamide in the treatment of acute diarrhoea in adults. There is no evidence that it offers any benefit in terms of improved or more rapid response rates but there is some evidence that it may be associated with a reduced incidence of rebound constipation (10% in absolute terms).

Current advice (BNFC) is not to use any anti-motility agents in children aged under 12 years with acute diarrhoea. Similarly NICE do not support their use.

There is good evidence that racecadotril is superior to supportive treatments alone in speed of treatment response rates in children but no evidence that it is any more effective or better tolerated than loperamide.

Loperamide and ORS are very widely prescribed in the NHS and any change in practice which involved use of a more expensive preparation could have major cost implications (estimated ~ £10,000 per 100,000 population)

There is no robust evidence to suggest that racecadotril is a cost-effective use of NHS resources.

### Limitations of review

The actively controlled trials in adults are poorly described in terms of trial design, methodology and powering and some use a sub-optimal dose of loperamide as a comparator.

There has been only one actively controlled trial conducted in children (against loperamide), other data are derived from trials assessing the impact of adding racecadotril to supportive treatments.

In both adults and children the trials have been conducted in a range of countries and this may impact on generalisability to the UK.

The trials in children do not appear to have assessed potentially more important clinically relevant end-points such as need for further healthcare intervention (hospital admissions, IV hydration, GP visit etc). Very few of the studies were carried out in older children – the median age in the meta-analysis was 12 months and again this limits the generalisability of the findings.
References/ Sources of Review

1. Hidrasec Summary of Product Characteristics
   100mg hard capsules, 10mg and 30mg granules for Summary of Product Characteristics. Abbott Healthcare September 2011.


Appendix 1- Search Strategy

The literature discussed in this review was identified in recently published reviews by NICE/NPC, SMC supplemented by a rapid search of Embase and Medline.
### Bedfordshire and Luton Joint Prescribing Committee (JPC)  
Assessment against Ethical and Commissioning Principles

**Treatment assessed (April 2013):**
Racecadotril for the symptomatic treatment of acute diarrhoea in adults and children aged over 3 months

**JPC Recommendation**
The use of racecadotril is not recommended.

1) **Clinical Effectiveness**
   - Adults: there is some relatively poor quality evidence to show that racecadotril is similarly effective to loperamide in adults and may cause less rebound constipation.
   - Children: there is good evidence to show that racecadotril is more effective than placebo in reducing the percentage of children with diarrhoea 48 hours after starting treatment and limited evidence to suggest that it is similarly effective to loperamide.

2) **Cost Effectiveness**
   There is no robust evidence to suggest that use of racecadotril represents a cost effective use of NHS resources

3) **Equity**
   None identified

4) **Needs of the community**
   Anti-diarrheal agents and ORS are widely prescribed and are also available to purchase in pharmacies

5) **Need for healthcare (incorporates patient choice and exceptional need)**
   Not relevant

6) **Policy drivers**
   Not relevant

7) **Disinvestment**
   Not relevant

The JPC agreed the following sections within the CCG Ethical and Commissioning Framework were not relevant to JPC discussions: Health Outcomes, Access, and Affordability.
<table>
<thead>
<tr>
<th>Question</th>
<th>Step 1 (Level 5)</th>
<th>Step 2 (Level 4)</th>
<th>Step 3 (Level 3)</th>
<th>Step 4 (Level 2)</th>
<th>Step 5 (Level 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>How common is the problem?</td>
<td>Local and current random sample surveys (or censuses)</td>
<td>Systematic review of surveys that allow matching to local circumstances**</td>
<td>Local non-random sample**</td>
<td>Case-series**</td>
<td>n/a</td>
</tr>
<tr>
<td>Is this diagnostic or monitoring test accurate? (Diagnosis)</td>
<td>Systematic review of cross sectional studies with consistently applied reference standard and blinding</td>
<td>Individual cross sectional studies with consistently applied reference standard and blinding</td>
<td>Non-consecutive studies, or studies without consistently applied reference standard**</td>
<td>Case-control studies, or &quot;poor or non-independent reference standard&quot;**</td>
<td>Mechanism-based reasoning</td>
</tr>
<tr>
<td>What will happen if we do not add a therapy? (Prognosis)</td>
<td>Systematic review of inception cohort studies</td>
<td>Inception cohort studies</td>
<td>Cohort study or control arm of randomized trial*</td>
<td>Case-series or case-control studies, or poor quality prognostic cohort study**</td>
<td>n/a</td>
</tr>
<tr>
<td>Does this intervention help? (Treatment Benefits)</td>
<td>Systematic review of randomized trials or n-of-1 trials</td>
<td>Randomized trial or observational study with dramatic effect</td>
<td>Non-randomized controlled cohort/follow-up study**</td>
<td>Case-series, case-control studies, or historically controlled studies**</td>
<td>Mechanism-based reasoning</td>
</tr>
<tr>
<td>What are the COMMON harms? (Treatment Harms)</td>
<td>Systematic review of randomized trials, systematic review of nested case-control studies, n-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect</td>
<td>Individual randomized trial or (exceptionally) observational study with dramatic effect</td>
<td>Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**</td>
<td>Case-series, case-control, or Historically controlled studies**</td>
<td>Mechanism-based reasoning</td>
</tr>
<tr>
<td>What are the RARE harms? (Treatment Harms)</td>
<td>Systematic review of randomized trials or n-of-1 trial</td>
<td>Randomized trial or (exceptionally) observational study with dramatic effect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is this (early detection) test worthwhile? (Screening)</td>
<td>Systematic review of randomized trials</td>
<td>Randomized trial</td>
<td>Non-randomized controlled cohort/follow-up study**</td>
<td>Case-series, case-control, or Historically controlled studies**</td>
<td>Mechanism-based reasoning</td>
</tr>
</tbody>
</table>

* Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

** As always, a systematic review is generally better than an individual study.

How to cite the Levels of Evidence Table

* CCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornhill, Ollie Goddard and Mary Hodgkinson