racecadotril 10mg, 30mg granules for oral suspension (Hidrasec Infants®, Hidrasec Children®)
SMC No. (818/12)
Abbott Healthcare Products Ltd

09 November 2012

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

**ADVICE**: following a full submission

**racecadotril (Hidrasec Infants®, Hidrasec Children®)** is not recommended for use within NHS Scotland.

**Indication under review**: Complementary symptomatic treatment of acute diarrhoea in infants older than three months and in children, together with oral rehydration and the usual support measures, when these measures alone are insufficient to control the clinical condition.

Racecadotril was significantly better than placebo in reducing mean stool output at 48 hours in children with acute diarrhoea treated in hospital. There is insufficient evidence that it improves recovery rate.

The submitting company did not present a sufficiently robust clinical and economic analysis to gain acceptance by SMC.

The licence holder has indicated their intention to resubmit.

Overleaf is the detailed advice on this product.

**Chairman,**
Scottish Medicines Consortium
**Indication**

Complementary symptomatic treatment of acute diarrhoea in infants older than three 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.

The presence of bloody or purulent stools and fever may indicate the presence of invasive bacteria as a reason for diarrhoea, or the presence of other severe disease. Also, racecadotril has not been tested in antibiotic-associated diarrhoea. Therefore, racecadotril should not be administered under these conditions.

The product must not be administered to children with renal or liver impairment, whatever the degree of severity, due to a lack of information on these patient populations. Because of possible reduced bioavailability, the product must not be administered in cases of prolonged or uncontrolled vomiting.

**Dosing Information**

1.5mg/kg three times daily. Treatment should be continued until two normal stools are recorded but should not exceed seven days.

The granules can be added to food, dispersed in a glass of water, or in the feeding bottle, mixing well, and followed by immediate administration.

**Product availability date**

17 October 2012

**Summary of evidence on comparative efficacy**

Acute diarrhoea is the main symptom of gastroenteritis and most episodes in children in Scotland are mild and can be treated at home, although annually around 10% of children under five years require treatment from a healthcare service. Rotavirus is the leading cause of severe, dehydrating gastroenteritis among children and almost all children in both industrialised and developing countries have been infected by the age of five. Although vaccines are available in the UK, children are not routinely immunised against this virus.

Racecadotril is the first in a new class of drugs for acute diarrhoea that reduce intestinal secretion of water and electrolytes by inhibiting the breakdown of encephalins which are endogenous opioid peptides. It does not increase intestinal transit time. Racecadotril is licensed to be used in addition to oral rehydration treatment (ORT) when this and the usual support measures are insufficient to control the condition.

Although the submitting company presented eight clinical studies of racecadotril in children with acute diarrhoea, only the randomised studies that were performed in Europe are assessed.
A randomised, double-blind, placebo-controlled study in France in the 1990’s enrolled children between 3 months and 4 years who required hospital admission for acute diarrhoea, (at least three watery stools per day), that had lasted less than 72 hours. The children were randomised, stratified by gender, to receive racecadotril 1.5mg/kg (n=89) or placebo (n=83) orally three times daily for five days or earlier if the child had recovered, i.e. passed two formed stools or no stool for 12 hours. All patients received rehydration either orally or via a nasogastric tube. If intravenous (iv) rehydration was required for less than 12 hours, the patient could be included in the study when this was completed. Patients stayed in hospital for at least 48 hours.

The primary outcome was mean stool output at 48 hours, as grams (g) per hour, calculated by dividing the total output by the number of hours (maximum of 48) till recovery. Analyses were performed on the full data set which included all patients with data available: 84 receiving racecadotril and 82 receiving placebo. The per protocol (PP) population included only those patients that could be fully evaluated: 58 receiving racecadotril and 63 receiving placebo. In both analyses the primary outcome was significantly improved in the racecadotril group compared with placebo. The results were from published graphs. For the full data set the stool output rate was 9g/hour versus 15g/hour, respectively with an estimated ratio of 60% (95% confidence interval [CI]: 43% to 88%). For the per-protocol population the stool output rate was 8g/hour versus 16g/hour, respectively with an estimated ratio of 50% (95% CI: 33% to 75%). A significant reduction in stool output with racecadotril was also reported at 24 hours, a secondary outcome. However racecadotril did not improve recovery rate at five days which was reported according to gender and was numerically lower for racecadotril than placebo. The proportion of males that had recovered by five days was 88% versus 90% and of females was 79% versus 82%, respectively. Statistical significance was not reported.

A randomised, open-label controlled study in children treated as hospital outpatients was carried out in Spain in 2005 to 2006. Patients were enrolled if aged between 3 months and 3 years with acute gastroenteritis defined as at least three loose stools in the previous 24 hours. In total 188 children were randomised equally and received racecadotril plus ORT or ORT alone every eight hours at doses of 10mg if weight less than 9kg; 20mg if weight between 9 and 13kg; 30mg if weight more than 13kg. Treatment with racecadotril was stopped when the child had two bowel movements of normal consistency or had no bowel movements for 12 hours or after seven days, whichever came first.

The intention to treat (ITT) analysis included 88 and 91 patients in the treatment and control groups, respectively and the PP analysis included 69 and 64 in the treatment and control groups, respectively. The published report did not define the ITT and PP populations but noted that the same results were obtained in each.

The primary outcome was the average number of bowel movements at 48 hours and was not significantly different between the racecadotril plus ORT and ORT groups: 3.8 versus 4.1, although it is not clear if these results are from the ITT or PP analysis. There was no significant difference between racecadotril plus ORT and ORT in the following secondary outcomes: average duration of diarrhoea was 4.0 versus 4.7 days, respectively and subsequent visits to the emergency department or doctor by day seven, 17 versus 19, respectively.

A single centre open-label randomised controlled study in France in 2001 included 164 children from 3 months to 3 years with acute diarrhoea (at least three liquid stools in the previous 12 hours) who were randomised alternately to receive study treatment or not. Study treatment comprised racecadotril three times daily at doses of 10mg if ≤9kg and 20mg if >9kg body weight
until cessation of diarrhoea (no stools for at least 12 hours) for up to seven days. If weight loss was <5% ORT was given at home; if >10% they received iv rehydration in hospital. If weight loss was between 5% and 10% they initially received ORT in the emergency department and were reviewed after four hours and depending on prespecified criteria, were discharged or admitted to hospital for ORT or iv rehydration as required.

The primary outcome was the number of medical examinations (by the treating physician or at hospital) during the week after starting treatment and was analysed in the PP population (n=154) that excluded three children in the racecadotril group and seven in the control group who did not respond to telephone calls by day seven. The racecadotril group had significantly fewer additional medical visits than the control group between days two and seven: 18% (14/76) versus 35% (27/78). No meaningful conclusion could be drawn regarding the reasons for the additional visits as the published report cited the most common reason as “same episode of diarrhoea”. Also more than one reason was recorded per child. These additional medical visits resulted in hospital admission in two patients in the racecadotril group and in eight patients in the control group. The secondary outcome of duration of diarrhoea was significantly shorter in patients treated with racecadotril compared with control, 97 hours versus 138 hours, respectively. The mean number of stools produced during the first 48 hours was 6.8 in the racecadotril group versus 9.5 in the control group, (p <0.001). The average weight gain was similar in the racecadotril and control groups: 4.4% versus 3.5%, respectively.

Quality of life was not investigated in any of the above studies.

**Summary of evidence on comparative safety**

In the French randomised blinded inpatient study and the Spanish outpatient study described above, a similar number of adverse events was reported for racecadotril and control.

The Summary of Product Characteristics (SPC) for racecadotril gives clinical study safety data for the treatment of acute diarrhoea by racecadotril in 685 children and by placebo in 411 children. The frequency of adverse events was 15% in patients treated with racecadotril and 23% in the placebo groups. All adverse events were mild or moderate in severity. The most frequently occurring adverse events for racecadotril versus placebo, respectively, were vomiting (7.9% versus 9.2%), fever (3.2% versus 7.3%) and respiratory disorder (1% versus 1.5%).

Racecadotril sachets contain saccharose and are contraindicated in children with fructose intolerance, glucose malabsorption syndrome, and saccharase-isomaltase deficiency. The saccharose content should be taken into account in children with diabetes.

**Summary of clinical effectiveness issues**

Racecadotril has been available for use for many years in some countries in Europe and beyond. Four studies carried out in India and Central and South America were presented in the company submission but were not assessed in detail due to major differences from Scottish practice.

There is a lack of evidence of benefit with racecadotril in the studies that are most relevant to the Scottish situation, the French randomised blinded inpatient study and the Spanish...
randomised outpatient study.\(^2\) In patients receiving ORT the addition of racecadotril reduced mean stool output at 48 hours more than control in the inpatient study but not in the outpatient study. The clinically important secondary outcomes of recovery rate or duration of diarrhoea were not achieved in either study.

All three studies assessed above had limitations. The primary outcome of stool output in terms of weight (hospitalised patients) or number of bowel movements (outpatients) is a surrogate outcome and there are difficulties associated with accurately measuring stool output in young children, including the complication of separation of urine. The outcome of additional medical visits is also a surrogate and is not validated. Other relevant clinical outcomes include improvement in hydration status, duration of diarrhoea, need for intravenous fluids, hospital admission and length of hospital stay. Two of the studies were unblinded. In the outpatient setting the administration of study treatment (including ORT) was carried out by parents as was the recording of bowel movements. Both of these factors are a potential source of error. The Spanish outpatient study\(^2\) had a high dropout rate; only 137 of 188 (72\%) treated patients returned at the 48 hour visit and only 103 (55\%) returned at the 7 day visit. It is possible that the study therefore had insufficient power and it is not known how missing data were dealt with. In this study all except one child had mild dehydration and it is not clear that this population was sufficiently ill to warrant treatment with racecadotril within its licensed indication. In the Spanish study 60\% of children received concomitant medication but details were not reported.

The source of clinical efficacy data used in the economic case is a post hoc sub-group of the study investigating additional medical visits.\(^3\) In the ITT population 54\% (44/81) in the racecadotril group and 58\% (48/83) in the control group received initial oral rehydration and additional medical visits were made in 23\% (10/44) of racecadotril patients who had initial ORT and in 31\% (15/48) of control patients who had initial ORT. The number of additional medical visits used in the economic case is taken from the PP analysis that excluded three children in the racecadotril group and seven in the control group due to missing data; 24\% (10/41) versus 36\% (15/41), respectively.

The upper age limit in the clinical studies was three or four years and no evidence was submitted for the use of racecadotril in older children although the economic case includes children up to 11 years.

Racecadotril is licensed for treatment up to seven days duration and it would be helpful to have had follow up data beyond this time; however the studies described above completed follow up on day seven.

There have been no studies with racecadotril in the UK. Clinical experts consulted by SMC have advised that the current practice of rehydration, (usually oral) is sufficient in almost all cases of acute diarrhoea in children. A medicine that shortened the duration of diarrhoea because of an anti-secretory action could be a useful addition to the management of acute diarrhoea, however the evidence from the racecadotril studies most relevant to Scottish clinical practice have not shown this benefit.

Most UK and international guidance advises that further research is needed to determine the place of racecadotril in therapy.
Summary of comparative health economic evidence

The submitting company performed a cost-utility analysis of racecadotril with oral rehydration therapy compared to oral rehydration therapy alone for the treatment of acute diarrhoea in infants and children from 3 months to 11 years. The comparator was considered relevant. The economic model consisted of a decision tree analysis in which patients visited a GP for acute diarrhoea, with a probability of referral to secondary care. If the child was not referred, patients have a probability of consulting the GP for a second time with a subsequent probability of referral to secondary care. The time horizon was 6 days representing an episode of acute diarrhoea with associated GP and hospital care.

Data on the probability of referral to secondary care was for Scottish patients from a UK general practice database, estimated at 10.3% and 20.3% of episodes (with each episode assumed to represent one patient) following first and second GP consultation respectively. These probabilities were applied to both treatment arms. The difference in effectiveness of racecadotril was associated with a reduced probability of requiring a second GP consultation for the acute diarrhoea episode. GP re-consultation rates with ORT were estimated at 14% derived from the GP database. A relative risk of 0.67 for GP re-consultation was applied based on data on hospital consultations after initial treatment for acute diarrhoea derived from the racecadotril clinical trial conducted in a French hospital setting\(^3\). This outcome was used as a proxy for GP re-consultation in the model on the grounds that at the time in France there was no requirement to visit a GP for referral to secondary care. The data were from a sub-group of patients in the study who were receiving oral replacement therapy, representing 54% of the whole study population.

Costs included drug acquisition costs for racecadotril and the comparator ORT, which was assumed to be Dioralyte®. Treatment duration was assumed to be 4 days. Resource use estimates consisted of GP visits and hospital inpatient admittance after referral from the GP. The unit cost of a GP visit was estimated at £36 and each hospital inpatient stay was assumed to last 2 days (at a unit cost of £975 per day) and a diagnostic test was assumed to be performed at GP re-consultation in 10% of patients in order to determine the cause of the diarrhoea. Utilities for severe diarrhoea with hospitalisation and moderate diarrhoea with GP consultation (0.31 and 0.73 respectively) were based on a published study in acute rotavirus in infants aged >5 years. A utility of 0.94 for resolved diarrhoea was based on the UK general population value for people aged <25 years. These values were combined with the probability and estimates of time spent in each state in order to estimate quality adjusted life year (QALY) outcomes. No costs or disutilities associated with adverse events were considered, although this seems reasonable given the safety profiles of racecadotril and ORT.

The base case result was that racecadotril was less costly than ORT alone with a saving of £889 per 100 children cohort, but with an estimated QALY gain of 0.0067 per 100 children. The cost savings for racecadotril in the base case were driven by an estimated 5% fewer GP reconsultations and a consequent 1% fewer hospital referrals.

There were a number of key limitations with the analysis:
- The model structure was inappropriate in that the first referral to hospital was not related to the GP decision to prescribe racecadotril or ORT, and hence its inclusion appears redundant. Only drug costs associated with the 89.7% of patients not referred to
hospital at first GP consultation have been included and hence this would appear to represent the appropriate starting point in the model.

- Most of the analysis presented in the company submission relates to children in the age range 3 months to 5 years, and the clinical and utility data do not support analysis in children aged 5 to 11 years.

- The relative risk of 0.67 for second GP consultation with racecadotril treatment is non-significant and based on weak clinical evidence (as described in the clinical effectiveness section above). This difference completely drives the QALY benefit associated with racecadotril in the economic model, so when a relative risk of 1 was assumed for GP re-consultation due to the non-significant difference in the relative risk the outcome was an incremental cost associated with racecadotril and zero QALY gain.

- The company has assumed that data on referrals to secondary care equate to actual hospital admission, but it is possible that not all referrals will result in hospitalisation. This may bias the analysis in favour of racecadotril.

- The economic analysis assumed a patient weight of 13.5kg for determining drug acquisition costs for racecadotril, which represents a child aged about 2 years and so is too low for the patient age range covered of up to 11 years. Sensitivity analysis showed ICERs exceeding £30k/QALY for patient weight above 25 to 30kg. As such, the company was requested to provide a revised base case using an appropriate average weight to be more reflective of all patients covered by their model, estimated at be 17.27kg by the company. This led to reduced cost savings of -£563 per 100 children cohort. However, these results were based on assumptions regarding how doses of racecadotril are given in clinical practice which may underestimate quantities and thus which would require further validation before they can be accepted.

- There is uncertainty over the duration of drug treatment and length of hospital stay assumed for acute diarrhoea. Additional sensitivity analysis requested from the company demonstrated incremental cost effectiveness ratios (ICERs) exceeding £30k/QALY for scenarios based on the use of 9 sachets and either duration of racecadotril and ORT exceeding 5 days, or a hospital stay of 1 day assumed.

- There is uncertainty over the reliability of the utility values assumed in the model. However, it is difficult to robustly estimate utilities in infants and young children by other means. In addition, the utility estimate for resolved diarrhoea from the general population may overestimate or at least not relate well to children aged 0 to 11 immediately after an episode of acute diarrhoea.

Hence, due to the weakness of the clinical evidence used in the economic analysis and several other limitations, the economic case in children aged 3 months to 11 years has not been demonstrated.

**Summary of patient and public involvement**

A Patient Interest Group Submission was not made.
Although not yet marketed in the UK, racecadotril has been available for use for many years in some countries: (eg in France from 1999 and in India from 2001).

The most recent World Health Organisation (WHO) Model List of Essential Medicines for Children (intended for use for children up to 12 years of age) was published in 2011 and does not include racecadotril. Recommended treatments for diarrhoea are oral rehydration salts and zinc sulphate, (due to the prevalence of zinc deficiency in malnourished children). An application to add racecadotril to the essential list of medicines had been assessed and rejected by WHO in 2007. The evidence presented was from two hospital-based studies, in Peru and in France. The Expert Committee concluded that the evidence base was limited and that the value of racecadotril therapy outside of the hospital setting, and in less severely affected infants was not clear. Concerns were also raised about the possibility of unpublished negative trials.

In 2012 the World Gastroenterology Organisation published Global Guidelines; acute diarrhoea in adults and children: a global perspective. These guidelines state that ORT is a cost-effective method of managing acute gastroenteritis and it reduces hospitalisation requirements in both developed and developing countries. It states that in paediatrics, in general, anti-diarrhoeals have no practical benefits for children with acute or persistent diarrhoea. It notes that racecadotril is an encephalinase inhibitor (non-opiate) with anti-secretory activity that has been found useful in children with diarrhoea, and is now licensed in many countries in the world for use in children.

In 2009 the National Institute for Health and Clinical Excellence (NICE) published clinical guideline 84: Diarrhoea and vomiting in children. Diarrhoea and vomiting caused by gastroenteritis diagnosis, assessment and management in children younger than 5 years. The guidance states that anti-diarrhoeal treatments should not be used. It notes that racecadotril (at that time) was not licensed for use in the UK but was used elsewhere in Europe. It states that there was evidence that racecadotril had an antidiarrhoeal effect but further research is required to examine the possible clinical and health economic benefits that might be associated with its use in the UK.

In 2008 the European Society for Paediatric Gastroenterology, Hepatology and Nutrition/European Society for Paediatric Infectious Diseases published Evidence-based Guidelines for the Management of Acute Gastroenteritis in Children in Europe. It notes that racecadotril may be considered in the management of acute gastroenteritis. However, well-designed prospective studies of efficacy and safety should be carried out in outpatient children.

It states that in three relatively small randomised controlled trials with some methodological problems, two conducted in hospitalised children, in developed and developing countries, racecadotril was effective in reducing the volume and frequency of stool output and in reducing the duration of diarrhoea (particularly in children with rotavirus diarrhoea). There is evidence in favour of the use of racecadotril over placebo or no intervention to reduce the stool output in children with acute gastroenteritis. However, this evidence is based mainly on inpatient data, and does not take into account safety concerns that can be resolved either in studies involving large cohorts of children or in postmarketing surveillance evaluation, which is mandatory before therapy with racecadotril can be recommended.
In 2003 the Centers for Disease Control and Prevention, in their Morbidity and Mortality Weekly Report: Managing Acute Gastroenteritis Among Children, Oral Rehydration, Maintenance, and Nutritional Therapy, stated the following: Racecadotril, an encephalinase inhibitor, preserves the anti-secretory activity of encephalins and does not slow intestinal transit or promote bacterial overgrowth. Its use has demonstrated promise in two controlled clinical trials among children, among whom it significantly reduced stool output when compared with placebo. Although the majority of cases of acute diarrhoea require no adjunctive therapy, racecadotril might prove to be a useful adjunct. More studies are needed.

**Additional information: comparators**

Both loperamide and co-phenotrope (Lomotil®) are licensed for acute diarrhoea in children over four years. However current guidelines do not recommend the use of anti-diarrhoeals in children. Therefore there are no relevant comparators to racecadotril in children under 12 years.

**Cost of relevant comparators**

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<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost per course (£)</th>
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<td>racecadotril</td>
<td>Orally 1.5mg/kg three times daily</td>
<td>Up to 18</td>
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Costs are from the company submission and are based on up to 7 days treatment for the dose range for children aged 3 months to 11 years, one 10mg sachet three times daily to two 30mg sachets three times daily; the cost of racecadotril is the same for both strengths of sachets.

**Additional information: budget impact**

The submitting company estimated the population eligible for treatment to be 12,469 in all five years with an estimated uptake rate of 0.50% in year 1 and 39.80% in year 5. The gross impact on the medicines budget was estimated to be £1k in year 1 and £97k in year 5. As no other drugs were assumed to be displaced the net medicines budget impact is expected to remain as £1k in year 1 and £97k in year 5.
References

The undernoted references were supplied with the submission.


This assessment is based on data submitted by the applicant company up to and including 12 October 2012.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.