NICE advice

Acute diarrhoea in children: racecadotril as an adjunct to oral rehydration

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), BNF for children (BNFc) or the MHRA or NICE websites for up-to-date information.

Key points from the evidence

Racecadotril (Hidrasec) 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 complementary symptomatic treatment of acute diarrhoea in infants (aged over 3 months) and in children, together with oral rehydration and the usual support measures (dietary advice and increased daily fluid intake), when these measures alone are insufficient to control the clinical condition. It is also licensed for the symptomatic treatment of acute diarrhoea in adults, which is the subject of a separate evidence summary.

A meta-analysis (9 studies, n=1384) in children (median age 12 months) with acute diarrhoea has shown that racecadotril in combination with ORS solution statistically significantly reduces the duration of diarrhoea and the volume and frequency of stool output, and increases the proportion of children who recover within 2 days, compared with ORS solution alone or with placebo. The median duration of diarrhoea was 1.75 days in the racecadotril group and 2.81 days in the

comparator group ($p<0.001$). Four children would need to be treated with racecadotril rather than placebo for 1 extra child to recover in 2 days. It is unclear from this meta-analysis whether racecadotril reduces the risk of further inpatient or outpatient visits, or the need for intravenous rehydration.

The number of adverse events did not differ significantly between the groups. 11.6% of children in the racecadotril group had an adverse event compared with 10.1% in the comparator group (p value not stated).

The meta-analysis has several limitations and limited applicability to UK practice, particularly primary care. The majority of children in the UK recover from acute diarrhoea without treatment or by using ORS solution alone. Although adjunctive therapy with racecadotril appears to be effective and well tolerated, it is unclear which children would benefit from it and whether it is cost effective.

A UK cost-effectiveness analysis (Rautenberg et al. 2012) has been published. It is not discussed here because cost-effectiveness analyses are outside the scope for Evidence summaries: new medicines.

In December 2012, the Scottish Medicines Consortium did not recommend racecadotril for use in children in NHS Scotland. Having considered 3 studies carried out in Europe (which were included in the meta-analysis discussed in this evidence summary) it concluded that the clinical and economic analysis presented by Abbott Healthcare Products Limited was not sufficiently robust to gain acceptance.

Diarrhoea and vomiting caused by gastroenteritis: diagnosis, assessment and management in children younger than 5 years (NICE clinical guideline 84) covers diagnosis of gastroenteritis, assessment of dehydration, fluid management, nutritional management and the role of antibiotics and other therapies. Low-osmolarity oral rehydration salt (ORS) solution is recommended for children with dehydration and those at risk of dehydration. The guideline does not recommend using antidiarrhoeal drugs.

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

Key evidence

Lehert P, Chéron G, Calatayud GA et al. (2011) Racecadotril for childhood gastroenteritis: an individual patient data meta-analysis. Digestive and Liver Disease 43: 707–13

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.

The NICE clinical guideline on diarrhoea and vomiting in children under 5 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. One of the studies was carried out in a single centre in Peru (Salazar-Lindo et al. 2000, n=135) and the other was carried out in 13 centres in France (Cézard et al. 2001, n=172). The studies found that children under 4 years who were given racecadotril (1.5 mg/kg 3 times daily) and oral rehydration salt (ORS) solution had a statistically significantly reduced total and average hourly stool output 48 hours after starting treatment compared with children given placebo and ORS solution. 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.

The highest quality published evidence available at the end of 2012 is discussed in this evidence summary. Although a UK cost-effectiveness analysis (Rautenberg et al. 2012) has been published, it is not discussed here because cost effectiveness is outside the scope of Evidence summaries: new medicines.

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. Infective gastroenteritis is the most common cause of diarrhoea, with or without vomiting, in young children. Viral infections account for most cases in the developed world, although bacteria or protozoal pathogens may also be responsible. A European study found that approximately 10% of children under 5 years present to healthcare services with gastroenteritis each year. Rotavirus infection accounted for 28–52% of cases of

gastroenteritis identified (Van Damme et al. 2007). In the UK, from September 2013, oral vaccination against rotavirus will be offered to infants as part of their routine vaccination programme.

Parents often manage an episode of acute diarrhoea affecting their child at home, and in some cases without seeking professional advice. However, many parents and carers do seek advice from healthcare professionals. In a UK study (Armon et al. 2001), diarrhoeal illness accounted for 16% of medical presentations to a major paediatric accident and emergency department.

The NICE clinical guideline on diarrhoea and vomiting in children under 5 advises that the usual duration of diarrhoea is 5–7 days and in most children it stops within 2 weeks. Vomiting usually lasts 1 or 2 days and generally stops within 3 days. The guideline recommends that advice should be sought from a healthcare professional if a child's symptoms do not resolve within these timeframes or if signs or symptoms of dehydration develop.

In children who are not clinically dehydrated, the guideline advises that usual feeds, including breast or other milk feeds, should be continued, and that children should be encouraged to drink plenty of fluids (not including fruit juices and carbonated drinks). The guideline also recommends that children who are at increased risk of dehydration should be offered oral rehydration salt (ORS) solution (see the NICE clinical guideline for more information on assessing dehydration and shock).

The NICE clinical guideline on diarrhoea and vomiting in children under 5 advises that 50 ml/kg low-osmolarity ORS solution (240–250 mOsm/l) should be given over 4 hours, frequently and in small amounts, to children with clinical dehydration. The British national formulary (BNF) for children (December 2012) lists the following products with this composition: Dioralyte, Dioralyte Relief and Electrolade. Supplementation with usual fluids (including milk feeds or water, but not fruit juices or carbonated drinks) should be considered in children who refuse to take sufficient quantities of ORS solution and do not have red flag symptoms or signs (see table 1 of the guideline for more information). The guideline also recommends that nasogastric administration of ORS solution be considered in children who are unable to drink the solution or who vomit persistently.

The NICE clinical guideline on diarrhoea and vomiting in children under 5 also advises that intravenous fluid therapy should be used for clinical dehydration if shock is suspected or confirmed; if a child with red flag symptoms or signs shows clinical evidence of deterioration despite oral rehydration therapy; or if a child persistently vomits the ORS solution, given orally or through a nasogastric tube.

The guideline also advises that antidiarrhoeal medications should not be used. These include adsorbent agents (such as kaolin, smectite and activated charcoal), bismuth salicylate, antisecretory agents (including racecadotril, which was not licensed in the UK when the guideline was published) and antimotility agents. Although some antimotility agents such as loperamide syrup and co-phenotrope tablets are licensed in children aged 4 years and over, the BNF for children advises that they are not recommended for use in children aged under 12 years. The BNF for children also advises that antispasmodics and antiemetics should be avoided in young children with gastroenteritis because they are rarely effective and have troublesome adverse effects.

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 Hidrasec summaries of product characteristics for infants and children).

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 complementary symptomatic treatment of acute diarrhoea in infants (aged over 3 months) and in children together with oral rehydration and the usual support measures (dietary advice and increased daily fluid intake [Abbott Healthcare Products Limited: personal communication January 2013]), 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).

Racecadotril is also licensed for the symptomatic treatment of acute diarrhoea in adults (see the summary of product characteristics for more information). The evidence to support its use in adults is discussed in a separate evidence summary.

Course and cost

Racecadotril granules for oral suspension can be added to food or dispersed in water. The manufacturer does not advise dispersion in large amounts of water (a teaspoonful is sufficient) because this may prove problematic in infants and children and dissolving in large volumes may render it bitter (Abbott Healthcare Products Limited: personal communication January 2013).

The recommended dose is 1.5 mg/kg per dose (corresponding to 1 or 2 sachets per dose), 3 times daily at regular intervals. Racecadotril 10 mg sachets are intended for children who weigh less than 13 kg, and 30 mg sachets are intended for children who weigh 13 kg or more. Table 1 shows the recommended dosing regimen.

Table 1 Dosing regimen for racecadotril in infants (aged over 3 months) and children

Weight	Less than 9 kg	9 kg to less than 13 kg	13 to 27 kg	More than 27 kg
Dose (3 times a day)	10 mg	20 mg	30 mg	60 mg
Sachets per dose	1x10 mg	2x10 mg	1x30 mg	2x30 mg

Treatment should be continued until 2 normal stools are recorded and should not exceed 7 days.

The current NHS cost of racecadotril 10 mg and 30 mg is £8.42 for a pack containing 20 sachets (excluding VAT; costs taken from MIMS, February 2013). The cost of treatment depends on the weight of the child and the duration of illness.

Evidence review

This evidence review is based on a meta-analysis (Lehert et al. 2011) that assessed the efficacy of racecadotril as an adjunct to oral rehydration salt (ORS) solution, compared with ORS solution alone or with placebo in children with acute gastroenteritis (see table 2). The meta-analysis summarised the safety data by reporting the percentage of children experiencing an adverse event but the authors state that racecadotril safety was not an objective of the meta-analysis. Additional safety data have been obtained from the Hidrasec summaries of product characteristics for infants and children.

Racecadotril for childhood gastroenteritis: an individual patient data meta-analysis (Lehert et al. 2011)

- Design: an individual patient data meta-analysis of 9 randomised controlled trials, 4 in inpatients and 5 in outpatients. Trials were conducted in France, Guatemala, India, Mexico, Peru and Spain.
- Population: 1384 children aged from 1 to 71 months (median 12 months) with acute gastroenteritis and at least 3 watery stools in the previous 24 hours (mean number of diarrhoeic stools 8; mean duration of diarrhoea 41 hours).
- Intervention and comparison: racecadotril in combination with ORS solution (1.5 mg/kg 3 times per day in 8 studies, dose imprecise in 1 study) compared with ORS solution alone or with placebo for up to 7 days.
- Outcomes: using individual patient raw data from the studies, duration of diarrhoea and number of diarrhoeic stools were calculated for the period between first drug intake and the last unformed stool before recovery. Recovery was defined as the occurrence of 2 consecutive formed stools or no stool for 12 hours. Duration of diarrhoea was the primary end point. Stool output for the first 24 hours was considered for inpatient studies. Total number of diarrhoeic stools until recovery was considered for outpatient studies.

Table 2 Summary of the meta-analysis: Lehert et al. (2011)

	Racecadotril plus ORS	ORS alone or with placebo	Analysis[a]
Randomised	n=692	n=692	
Efficacy	n=692	n=692	
Primary outcome: median duration of diarrhoea	1.75 days	2.81 days	HR 2.04 (95% CI 1.85 to 2.32) p<0.001
Selected secondary outcomes:	n=692	n=692	
Responders (% with diarrhoea for less than 48 hours) after adjusting for baseline dehydration and rotavirus	50.3%	25.8%	RR 1.98 (95% CI 1.71 to 2.28) p value not stated NNT: 4

Stool output in first 24 hours (inpatient studies only n=637) (ratio of mean stool output racecadotril/ placebo)			GMR 0.59 (95% CI 0.51 to 0.74) p<0.001
Number of diarrhoeic stools until recovery (outpatient studies only n=695) (ratio of the mean number of diarrhoeic stools racecadotril/placebo)			RR 0.63 (95% CI 0.51 to 0.74) p<0.001
Safety[b]	n=698	n=695	
Children experiencing adverse events	11.6% (81/ 698)	10.1% (70/695)	No significant difference (p value not stated)

Abbreviations: CI, confidence interval; GMR, geometric mean ratio; HR, hazard ratio; NNT, number needed to treat; ORS, oral rehydration salt; RR, relative risk.

[a] Analysis was carried out on the intention to treat population of all children randomised. In 2 studies, some children were lost to follow-up: these were included assuming that therapy had been ineffective.

[b] It is unclear why the number of children in the safety population is higher than the number of children randomised.

Clinical effectiveness

The meta-analysis found that, when taken with ORS solution, racecadotril significantly reduced the duration of diarrhoea compared with ORS solution alone or with placebo. Median duration of diarrhoea was 1.75 days in the racecadotril group and 2.81 days in the comparator group: twice as many children recovered at any time with racecadotril (hazard ratio [HR] 2.04, 95% confidence interval [CI] 1.85 to 2.32). Overall, 50% of children taking racecadotril and ORS solution recovered within 48 hours, compared with 26% of children taking ORS solution alone or with placebo (relative risk [RR] 1.98, 95% CI 1.71 to 2.28). Four children would need to be treated with racecadotril rather than placebo for 1 extra child to recover in 2 days.

In the 4 inpatient studies, a statistically significant 41% relative reduction in stool output was seen in the racecadotril group compared with the comparator group. Similarly, in the 5 outpatient studies, racecadotril statistically significantly reduced the number of stools recorded by 37% in relative terms.

The efficacy of racecadotril for the primary outcome was found to be independent of the level of dehydration, the presence or absence of rotavirus, the age of the children, the setting (inpatient or outpatient) and the country or cultural context.

Safety

The number of adverse events did not differ significantly between the groups. 11.6% of children in the racecadotril group had an adverse event compared with 10.1% in the comparator group (p value not stated).

More than 27 million children have been treated with racecadotril in Europe and overall exposure is 32 million children worldwide (Abbott Healthcare Products Limited: personal communication January 2013). According to the summaries of product characteristics for infants and children, tonsillitis, rash and erythema have been reported more often with racecadotril than with placebo. However, these adverse effects are uncommon (frequency between 1 in 1000 and 1 in 100). The summaries of product characteristics for infants and children state that in studies during its clinical development racecadotril caused secondary constipation at a rate comparable to placebo.

Evidence strengths and limitations

The results of the meta-analysis showed that racecadotril plus ORS solution statistically significantly improves recovery rate and reduces the duration of diarrhoea and the volume and frequency of stool output compared with ORS solution alone or with placebo. However, it is unclear whether racecadotril reduces the rate of inpatient or outpatient visits, or the need for intravenous rehydration even though 3 unblinded studies (n=164, 170 and 179) included in the meta-analysis considered these outcomes.

The 9 studies included in the meta-analysis have various limitations, which affect its validity. For example, allocation concealment was judged adequate by the meta-analysis authors in only 3 studies, and only 5 studies were blinded. Follow-up was incomplete in 2 studies, but children lost to follow-up were included in the meta-analysis as therapy failure. There were heterogeneities in terms of inclusion criteria, treatment setting and study end points, although individual patient data were used to address heterogeneity for the end points studied in the meta-analysis.

The studies included in the meta-analysis were carried out in a range of developed and developing countries where the aetiology and severity of diarrhoea may differ, which may raise the applicability to UK practice. However, the meta-analysis found that the results for the primary outcome were independent of whether the studies were conducted in Europe or elsewhere.

The meta-analysis included hospital inpatient and outpatient studies of children with a range of baseline severities of acute diarrhoea. Some children received hospital treatment with intravenous fluids before racecadotril and/or ORS solution (Cojocaru et al. 2002 and Cézard et al. 2001).

Few studies have been carried out in older children. The median age of children in this meta-analysis was 12 months and the maximum age was 6 years.

A French study (Turck et al. 1999) compared the efficacy and safety of racecadotril and loperamide in 102 children aged 2 to 10 years (mean age 4.7 years) with acute diarrhoea (note, the BNF for children does not recommend loperamide in children aged under 12 years). The study concluded that racecadotril and loperamide were similarly effective in treating diarrhoea. There was no significant difference between the drugs in terms of number of diarrhoeic stools passed before recovery (mean 2.7 with racecadotril compared with 2.1 with loperamide) or duration of diarrhoea (mean duration 10.7 hours with racecadotril compared with 8.8 hours with loperamide). Adverse events were seen in 6 children (11.5%) taking racecadotril and 11 children (22%) taking loperamide. Statistically significantly more children taking loperamide had constipation (58% compared with 36.5%, p=0.03).

Context

Treatment alternatives

The NICE clinical guideline on diarrhoea and vomiting in children under 5 recommends low-osmolarity oral rehydration salt (ORS) solution for children with dehydration and those at risk of dehydration. Antidiarrhoeal drugs are not recommended by the guideline (although it should be noted that racecadotril was not available in the UK when the guideline was published in 2009). 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.

Costs of treatment alternatives

Drug	Age or weight of child	Usual dosage[a]	7-day cost excluding VAT[b]
Racecadotril sachets[c]	Less than 9 kg (3 months to 1 year)[d]	1x10 mg 3 times daily	£8.42[e]
	9 to less than 13 kg (about 1 to 3 years)[d]	2x10 mg 3 times daily	£16.84[e]

	13 to 27 kg (about 3 to 10 years)[d]	1x30 mg 3 times daily	£8.42[e]
	More than 27 kg (about 8 years and over)[d]	2x30 mg 3 times daily	£16.84[e]
Codeine phosphate[f,g]	12 years and over	30 mg 3 to 4 times daily	Oral solution 25 mg/5 ml £1.33 to £1.78[h] 30 mg tablets £1.12 to £1.49[h]
Co-phenotrope 2.5/ 0.025 mg tablets[f,g]	12 years	1 tablet 4 times daily	£3.01[h]
	13 to 16 years	2 tablets 3 times daily	£4.51[h]
Loperamide[f,g]	12 to 18 years	Usual dose 6 to 8 mg daily	Oral solution 1 mg/5 ml £2.46 to £3.28[h] 2 mg capsules £0.66 to £0.88[h] 2 mg tablets £1.51 to £2.01[h] 2 mg orodispersible tablets £5.86 to £7.81[h]

[a]The doses shown do not all represent the full range that can be used and they do not imply therapeutic equivalence.

[b]These costs will be additional to the cost of oral rehydration salt (ORS) solution because antidiarrhoeal drugs should generally be used as adjunctive therapy.

[c] Doses taken from the Hidrasec summaries of product characteristics for infants and children.

[d]Approximate values for age by weight taken from the BNF for children.

[e] Costs are for 20 doses (standard pack size) and are taken from MIMS February 2013.

[f] Doses taken from the BNF for children.

[g]Costs are not given for younger children when drugs are not licensed or not recommended in the BNF for children.

[h] Costs taken from Drug Tariff February 2013.

In children, racecadotril (and other antidiarrhoeal medication if appropriate) should be used with ORS solution. Therefore, ORS solution is not a treatment alternative and the cost is not given in this evidence summary.

Estimated impact for the NHS

Likely place in therapy

Racecadotril is 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 (dietary advice and increased daily fluid intake [Abbott Healthcare Products Limited: personal communication January 2013]), 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).

Although racecadotril plus ORS solution improves recovery rate and reduces the duration of diarrhoea and the volume and frequency of stool output more than ORS solution alone or with placebo, it is unclear where it fits within current UK practice. The majority of children in the UK recover from acute diarrhoea without treatment or by using ORS solution alone and it is unclear when or whether adjunctive therapy is necessary. It is also unclear whether the benefits of racecadotril are sufficiently clinically important to warrant the additional cost.

In 2009, the Guideline Development Group for the NICE clinical guideline on diarrhoea and vomiting in children under 5 concluded 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. In 2012, a cost–utility analysis (Rautenberg et al. 2012) was published that considers the cost effectiveness of racecadotril for acute diarrhoea in children from a UK perspective. This has not been evaluated here because cost-effectiveness is excluded from the scope for Evidence Summaries: new medicines.

In December 2012, the Scottish Medicines Consortium did not recommend racecadotril for use in children in NHS Scotland. Having considered 3 studies undertaken in Europe (which were included in the meta-analysis discussed in this evidence summary) it concluded that the clinical and economic analysis presented by Abbott Healthcare Products Limited was not sufficiently robust to gain acceptance. The company has indicated their intention to resubmit.

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 60,000 items of loperamide oral solution and orodispersible tablets were prescribed in primary care in England, at a cost of over £655,000. 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).

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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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