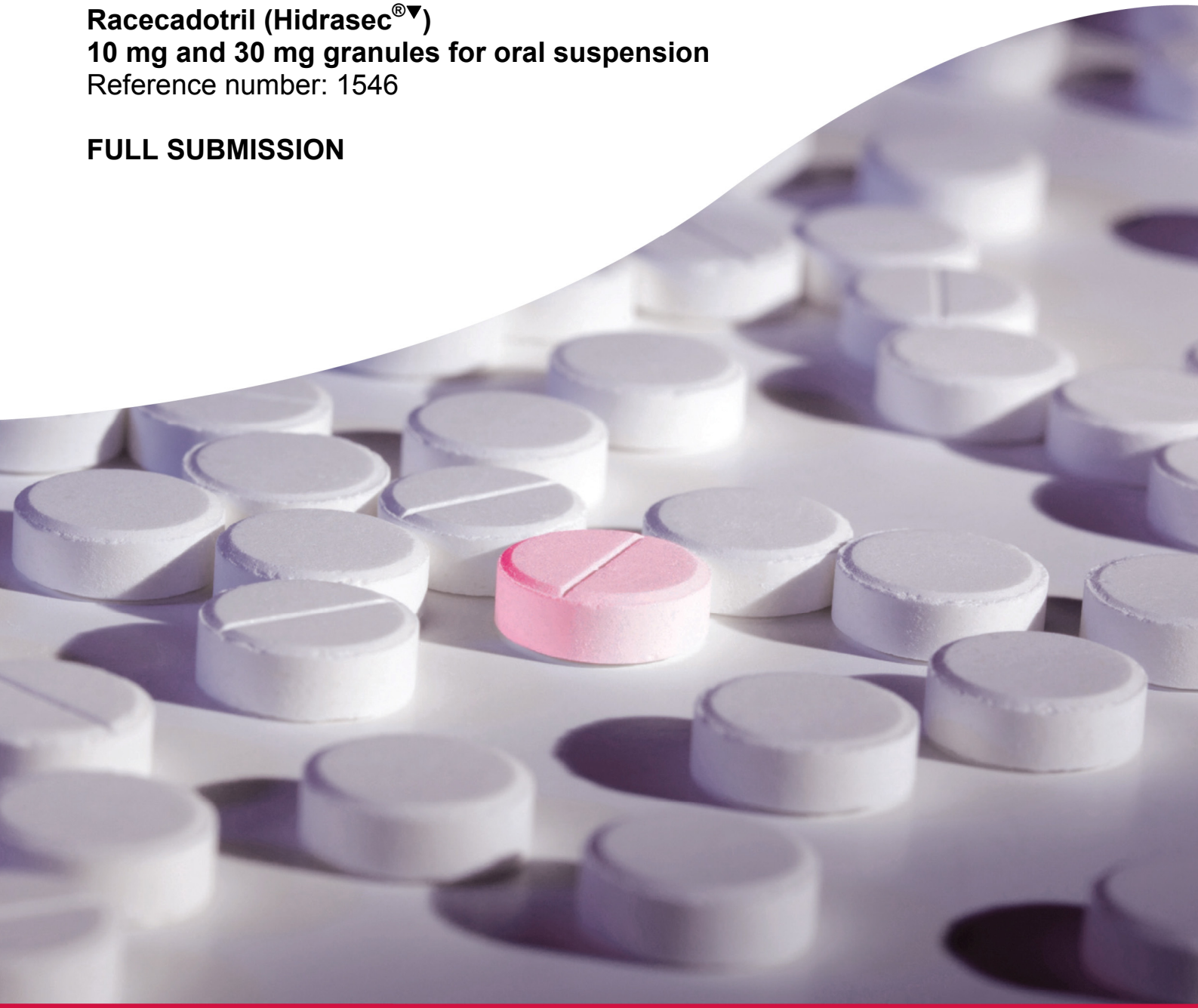
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Racecadotril (Hidrasec®▼)
10 mg and 30 mg granules for oral suspension
Reference number: 1546

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Racecadotril (Hidrasec®▼) 10 mg and 30 mg granules for oral suspension

This assessment report is based on evidence submitted by Abbott Healthcare Products Ltd on 14 September 2012[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Racecadotril (Hidrasec®▼) granules for oral suspension are indicated for the complementary 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. If causal treatment is possible, racecadotril can be administered as a complementary treatment[2,3].
Dosing	Dose is based on body weight and is rounded to the nearest number of whole sachets. The granules can be added to food, or dispersed in a glass of water or feeding-bottle. Treatment should continue until two normal stools are recorded, but duration of treatment should not exceed seven days. Refer to the Summaries of Product Characteristics (SPCs) for full details of dosing and treatment duration[2,3].
Marketing authorisation date	2 September 2011[4].
UK launch date	12 September 2012[2,3].

2.0 DECISION CONTEXT

2.1 Background

Diarrhoea and vomiting are the most common symptoms of gastroenteritis, an inflammation of the stomach and bowel, commonly caused by rotavirus in children[5,6]. Severe diarrhoea can quickly cause dehydration, which may be life threatening in young children and is a major cause of infant mortality in Africa and South East Asia[6,7]. In industrialised countries, diarrhoea is responsible for relatively few deaths, which occur mainly in the elderly; it is also a major cause of morbidity, giving rise to substantial health care costs[6,8]. Approximately 10% of children younger than five years present to healthcare services with gastroenteritis in the UK each year[6,7].

In the management of acute diarrhoea, the priority is prevention or reversal of fluid and electrolyte depletion[9]. Antimotility medicines such as loperamide (not recommended for children younger than four years) and codeine (not recommended for children younger than 12 years) may also be used to reduce the number of diarrhoeal episodes[9]. The National Institute for Health and Clinical Excellence (NICE) has published a Clinical Guideline for the treatment of diarrhoea and vomiting in children less than five years old. This recommends oral rehydration solution (ORS) for gastroenteritis and dehydration, and as a supplemental fluid for children without clinical dehydration, but does not recommend the use of antidiarrhoeal medicines in children aged less than five years[7].

Racecadotril decreases intestinal hypersecretion of water and electrolytes, exerting an antidiarrhoeal action without modifying the duration of intestinal transit. Racecadotril was granted a marketing authorisation in Spain in 2000 for capsules and in 2002 for granules, but was not licensed in the UK until 2011 (for both granules and capsules) due to the lack of a commercial partner in the UK[1]. The formulations under appraisal are two sachets providing 10 mg and 30 mg of racecadotril (as granules)[2,3]. Racecadotril is also available as 100 mg hard capsules, licensed for treatment of symptomatic diarrhoea in adults[10]. This indication/formulation has not been appraised by the All Wales Medicines Strategy Group (AWMSG)[11].

2.2 Comparators

The comparators requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) were ORS, codeine and loperamide.

The clinical and cost-effectiveness evidence provided in the company submission focuses on comparing racecadotril with ORS only; comparison of racecadotril with codeine or loperamide has not been provided. The company's rationale for this approach is that loperamide and codeine are not licensed for use in children aged less than 4 years and 12 years respectively[9]; and because current guidelines do not recommend the use of antidiarrhoeal medicines in children under 5 years[7].

2.3 Guidance and related advice

- NICE Clinical Guideline 84. Diarrhoea and vomiting caused by gastroenteritis: diagnosis, assessment and management in children younger than five years, full guideline (2009)[7].
- World Gastroenterology Organisation Global Guidelines. Acute diarrhea in adults and children: a global perspective (2012)[6].

AWMSG has issued the following advice for the use of racecadotril hard capsules:

- In the absence of a submission from the holder of the marketing authorisation, racecadotril (Hidrasec®) capsules cannot be endorsed for use within NHS Wales for the symptomatic treatment of acute diarrhoea in adults[11].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission describes nine randomised controlled trials (RCTs), conducted in six different countries in infants and children with acute diarrhoea, along with a meta-analysis of these studies. Limited information was available to the company for three of these trials (Gutierrez-Castrellon et al, Savitha et al and Melendez Garcia et al). The designs and results of the individual clinical studies are summarised in Table 1A, Appendix 1.

Inclusion criteria for the trials were the specific age ranges detailed in Table 1A and the presence of acute diarrhoea, defined by the passage of watery stools prior to study admission. Patients having chronic diarrhoea, prior treatment with an antidiarrhoeal medicine or an antibiotic were excluded[1].

3.1 Meta-analysis of racecadotril in childhood diarrhoea

The company submission includes a meta-analysis aimed at assessing racecadotril efficacy as an adjunct to ORS, compared to placebo and/or ORS in childhood acute gastroenteritis[12]. The analysis utilised data from the nine RCTs discussed in section 3.0 and summarised in Table 1A, Appendix 1, covering a total of 1,384 patients with an age range of 1–71 months and a median age of 12 months. Eight trials included patients with a median age of 10–18 months, with one trial having a higher median age of 32 months[12].

The presence of rotavirus and pathogens were recorded for all studies, with the exception of one trial, in which pathogens were only tested for children with stools containing blood. At baseline, the duration (± standard deviation) of diarrhoea was 40 ± 57 hours and 42 ± 39 hours for racecadotril plus ORS and ORS (with or without placebo) respectively[12].

The primary outcome was the duration of diarrhoea; secondary outcomes were the stool output during the first 48 hours for inpatients and the total number of diarrhoeic stools until recovery for outpatients. Duration of diarrhoea and the number of diarrhoeic stools were determined using the period between time of first treatment administration to time of last unformed stool before recovery, with recovery being defined as occurrence of two consecutive formed stools or no stool for 12 hours[12].

The median values for duration of diarrhoea, number of diarrhoeic stools and stool output by dehydration category are summarised in Table 1, stratified according to World Health Organisation classification and presence of rotavirus. The median duration of diarrhoea was 1.75 days for racecadotril plus ORS versus 2.81 days for ORS with or without placebo. Statistical analysis showed that more than two times more patients recovered at any time with racecadotril compared with ORS alone (hazard ratio = 2.04; confidence interval [CI]: 1.85, 2.32; $p < 0.001$). The mean ratio (racecadotril:placebo) of stool output (measured for inpatients only, n = 637) was 0.59 (CI: 0.51; 0.74; $p < 0.001$). The mean ratio (racecadotril:placebo) of the number of diarrhoeic stools (obtained for outpatients only, n = 695) was 0.63 (CI: 0.47, 0.85; $p < 0.001$)[12].

One study (Santos et al) found that racecadotril plus ORS did not improve the symptoms of diarrhoea, measured as the number of diarrhoeic stools over 48 hours, compared to ORS alone[13]. The study authors point out that other trials, in which racecadotril showed significant reduction in diarrhoea, were carried out on hospitalised children with more severe dehydration and more severe clinical manifestations. Moreover, in the hospital setting medication was given under direct supervision whilst in the study by Santos et al, physicians did not directly observe administration of the treatment[13].

Table 1. Duration of diarrhoea, stool output and number of diarrhoeic stools by dehydration category and presence of rotavirus[12].

		Rotavirus negative			Rotavirus positive		
Dehydration category:		**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Diarrhoea duration (days, ±SD)	Racecadotril + ORS	0.9±0.5	1.7±1.3	1.4±0.4	0.9±0.9	1.9±1.1	2.4±0.8
	ORS ± placebo	1.2±0.7	2.1±1.0	2.2±0.7	2.1±1.0	2.8±1.3	3.7±0.8
Number of diarrhoeic stools (±SD)	Racecadotril + ORS	6.5±4.0	5.5±4.5	13.0±6.1	8.9±5.9	5.7±4.3	8.4±7.3
	ORS ± placebo	8.8±4.4	9.2±4.0	10.1±3.0	10.7±5.4	11.8±5.3	11.0±4.9
Stool output (Kg ±SD)	Racecadotril + ORS	0.35±0.21	0.48±0.44	0.62±0.45	0.48±0.49	0.81±0.61	0.75±0.53
	ORS ± placebo	0.35±0.31	0.81±0.63	1.02±0.54	0.95±0.59	1.34±0.88	1.64±1.36
SD: standard deviation; ORS: oral rehydration solution							

3.2 Comparative safety

The company did not have access to the clinical study reports of all the RCTs, and thus safety data was drawn from overviews provided by Bioproject Europe Ltd (the sponsors of racecadotril) and the available published data. Safety data were provided for the following trials: Cézard et al[14], Salazar-Lindo et al[15], Álvarez Calatayud et al[16], Santos et al[13] and Gutierrez-Castrellon et al[1]. Vomiting was reported as an adverse event (AE) in the five trials for which data were available. In the meta analysis of the nine trials described in Section 3.1, there was no statistically significant difference in the number of patients with AEs between treatment groups (11.6% [81/698] for racecadotril and 10.1% [70/695] in the control group)[12]. Post-marketing analysis showed an individual case safety report occurrence of 1/338,000 from 14.54 million paediatric patients. Results from the post-marketing database showed the occurrence of AEs and AE withdrawals was not greater in patients treated with racecadotril plus ORS compared with ORS with or without placebo[1].

3.3 AWTTC critique

- NICE Clinical Guideline 84 does not recommend the use of antidiarrhoeal medication or routine use of antibiotics in children under five years with diarrhoea[7]. The company have used this guideline as justification for not including any evidence comparing racecadotril with loperamide in children with diarrhoea. However, the guideline only applies to children aged less than five years. Whilst the licensed indication imposes no definitive upper age range for treatment with racecadotril granules, the submitted cost-effectiveness model (see Section 4.0) considers infants and children aged 3 months to 11 years[1]. Loperamide is licensed for the treatment of patients aged 4 years and older[17].
- At the time of publication of NICE Clinical Guideline 84 (2009), racecadotril did not have a UK marketing authorisation. In response to queries from AWTTC on the applicability of this guideline to racecadotril, the company highlighted that a review of this guideline was conducted in 2012. The review concluded that recently published evidence[12,13] on the clinical effectiveness of racecadotril may warrant minor updates to the guideline; however as a number of other trials identified by the reviewers are still ongoing, it was considered premature to update the Clinical Guideline at the time of review.

- No comparison of racecadotril against codeine has been provided. The company do not consider codeine a suitable comparator as it is not licensed for use in children under the age of 12 years.
- The company has submitted clinical evidence for the use of racecadotril plus ORS, compared to ORS with or without placebo in children aged 1–71 months (median age 12 months) with acute diarrhoea[1]. Two studies were available using racecadotril in older children: one large uncontrolled trial in children aged 3 months to 12 years[18] and one versus loperamide in children aged 2–10 years[19]. The company did not include the latter trial in their submission because the lowest age of patients in the trial was below the age limit recommended for loperamide use in the UK[17]. In the meta analysis of nine RCTs, (n = 1,389) racecadotril plus ORS was shown to reduce diarrhoea (duration, stool output and stool number) compared to ORS with or without placebo[12]. The meta analysis found no influence of age or weight on racecadotril effectiveness[12], but it is not clear to what extent, if at all, these results can be extrapolated to older children[1].
- The majority of the trials were conducted in paediatric emergency departments, rather than in primary care settings. The company contend that at the time the studies were conducted the emergency departments in mainland Europe were used in a similar way to the primary care setting in Wales[1].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost utility analysis (CUA) of racecadotril granules for oral suspension for complementary symptomatic treatment of acute diarrhoea in infants (older than 3 months), and in children, together with ORS[1]. The comparator is ORS only; the company rationale for using this comparator is outlined in Sections 2.2 and 3.3. Comparative economic evidence of racecadotril with other comparators requested by AWTTC (see Section 2.2) has not been provided.

The analysis is based on a decision tree representing a single episode of acute diarrhoea. Patients enter the model on presenting to primary care with an acute diarrhoea attack. The patient is prescribed either ORS alone, or ORS plus racecadotril. They can either be referred to secondary care or managed in primary care. Patients not referred to secondary care will continue treatment for an average of four days after which they may return to their general practitioner (GP) for reconsultation if their diarrhoea has not resolved. Patients who reconsult their GP can be either referred to secondary care or considered to receive no further treatment. Patients referred to secondary care are assumed to spend two days, as inpatients, after which their diarrhoea resolves. The time horizon of the analysis is six days.

Effectiveness data are taken from a subgroup analysis of an RCT of racecadotril plus ORS versus ORS only, which assessed reconsultation rates to emergency departments in France[20], and from analyses of ORS use and outcomes data from a UK GP prescribing database (Cegedim Strategic Data, CSD)[21]. Parameters relating to the mean duration of hospital stay and the proportion of children having a diagnostic test are informed by clinical expert opinion. Utility values used in the model are based on a UK study[22].

The costs considered in the analysis included medication acquisition for ORS and racecadotril, and primary and secondary care use, including GP consultations, diagnostic tests and the cost of a two-day inpatient stay for each secondary care referral. No adverse event costs or disutilities were considered in the analysis. Unit

costs are sourced from standard UK sources including the British National Formulary (BNF)[17] and Personal Social Services Research Unit (PSSRU) unit costs[23].

4.1.2 Results of the company's analyses

The results of the company's base case analysis, based on a hypothetical cohort of 100 patients, are presented in Table 2. These suggest that using racecadotril plus ORS dominates the use of ORS only (therefore racecadotril plus ORS is more effective and less costly than ORS alone), driven by modelled differences in rates of reconsultation and referral to secondary care.

Table 2. Base case analysis results (per 100 patients)

	Racecadotril+ORS	ORS only	Difference
Total medication costs	£1,272	£396	£876
Total reconsultation costs	£261	£390	-£129
Total referral costs	£29,811	£31,912	-£2,101
Total costs	**£31,345**	**£32,699**	**-£1,354**
Total QALYs	**1.2896**	**1.2832**	**0.0065**
ICER (£/QALY gained)	Racecadotril+ORS more effective and less costly than ORS only		
ORS: oral rehydration solution; QALY: quality-adjusted life-year gained; ICER: incremental cost effectiveness ratio.			

Sensitivity and scenario analyses indicate that the model is most sensitive to the assumed relative risk of referral to secondary care at first consultation (after racecadotril plus ORS or ORS alone has been prescribed). Use of reconsultation rates from a meta-analysis of trials conducted in primary and secondary care[12] generates the same results as the base case analysis, but has the same limitations as those discussed in Section 4.1.3. Reducing the risk of referral to secondary care with racecadotril increases modelled cost savings and quality adjusted life year (QALY) gains. Threshold analyses are presented in Table 3.

Table 3. Threshold analyses

Parameter	Value required for racecadotril to remain cost-effective according to a threshold cost per QALY of:		Plausibility of exceeding threshold cost/QALY
	£30,000	£20,000	
Relative risk – reconsultation	0.8808	0.8775	These values appear plausible given the uncertainty in this parameter
Relative risk – referral at second GP consultation	1.3504	1.3396	Assumes racecadotril increases risk of referral compared with ORS. Not plausible?
Cost per sachet of racecadotril	£1.16	£1.13	Not plausible based on current list price?
Duration of hospitalisation (days)	0.53	0.59	Not plausible for an admission of less than one day?
QALY: quality-adjusted life-year gained.			

4.1.3 AWTTC critique

The economic evidence submitted by the company only compares racecadotril against ORS; other comparators requested by AWTTC have not been considered (see Sections 2.2 and 3.3 for company justification for this approach). Additionally, no evidence was submitted to support the use of racecadotril when causal treatment is possible. The patient population in the RCT used as a main source of the efficacy estimates[20], may not reflect typical patients presenting in primary care in Wales (see

explanation below), and the sub-group analysis conducted to provide relative reconsultation rates showed no statistically significant difference between racecadotril plus ORS and ORS alone. The model is sensitive to the assumed risk of reconsultation. Collectively, it is uncertain whether the results of the cost utility analysis will adequately reflect the cost effectiveness of racecadotril use in clinical practice.

Strengths of the economic evidence:

- The company has provided a wide range of sensitivity, scenario and threshold analyses to characterise the parameter uncertainty around the base case analysis.

Limitations of the economic evidence:

- It is not clear whether the structure of the decision tree model adequately reflects the licensed indication of racecadotril. Whilst the indication places racecadotril as an add-on to ORS when ORS alone is not effective, the economic model represents a clinical pathway in which racecadotril is prescribed together with ORS at first presentation, where the alternative treatment is ORS alone.
- The company has selected one study to reflect relative effectiveness on the basis that only this study provides relevant reconsultation rates[20]. This was an open label RCT conducted in France in children aged 3 months to 3 years. Visits to the emergency department are used as a proxy for visits to primary care physicians (GPs). The company asserts that patients in the trial would have been equally likely to visit the GP or the emergency department. However, it is plausible that patients taken to the emergency department would have more severe or faster deteriorating acute diarrhoea than those taken to a GP. Hence, the patient population in this study may not be representative of the target population in terms of severity.
- The relative risk (RR) of reconsultation for racecadotril plus ORS versus ORS alone was based on a subgroup analysis and was not statistically significant (RR 0.67; AWTTC estimated 95% CI 0.34 to 1.31). This key parameter is therefore subject to significant uncertainty, and threshold analysis showed that plausible values of 0.8775 and 0.8808 would generate ICERs of £20,000 and £30,000 per QALY gained, respectively (see Table 3). However, it should also be noted that the modelled scenario reflects very small QALY differences over a short time horizon of analysis; small changes in the QALY estimates can lead to large changes in the ICER.
- The SPC notes that treatment duration in clinical trials was five days; however, the treatment duration assumed in the model was four days[3]. This would bias the results in favour of racecadotril, although in one-way sensitivity analysis exploring up to six days of treatment (but retaining all other assumptions in the base case analysis), racecadotril remained dominant.
- The cost of inpatient stay was based on Information Services Division Scotland data[24] and is somewhat greater than that assumed in a recent published economic analysis of racecadotril undertaken from a UK NHS perspective[25]. However, racecadotril plus ORS remained dominant over ORS when inpatient costs were explored in the range ±25% of the base case value.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC identified a published CUA of racecadotril plus ORS versus ORS alone, conducted from the UK NHS perspective and funded by the applicant company[25]. This analysis had a similar clinical pathway and time horizon of analysis to the current CUA , but the study by Cojocaru et al[20], used in the current analysis to model reconsultation rates, was rejected for use on the basis that it does not reflect the primary care use of racecadotril being modelled[25]. Instead, it is assumed that patients not responding at 48 hours, as estimated in a meta-analysis of nine trials, represent reconsultation rates (although it should be noted that several of

these studies were also conducted in secondary/tertiary care settings)[12]. A study of racecadotril, conducted in boys attending the emergency room in Spain, is used to model secondary referral rates[16]. The source of utility values is reported to be the same in the current study and the published study; however, the current study assumes utility values for health states in secondary care that represent a poorer quality of life for children than those in the published analysis (0.31 versus 0.61, respectively). There are also differences in: the assumed length of stay for those referred to secondary care, which is longer in the published study (2.65 days versus 2 days); and the associated unit costs, which are lower in the published study (£523 versus £975 per day). However, as in the current analysis, the published study still concludes racecadotril plus ORS is marginally more effective and associated with lower overall costs compared with ORS alone[25].

5.0 SUMMARY OF THE EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company submission reports that in 2010, based on data from Cegedim Strategic Data (CSD), there were 98,852 episodes of acute diarrhoea in infants and children under 12 years in Wales, of which 16,880 episodes were treated with ORS[1]. Assuming a constant incidence over the next five years, the company estimated that there will be a total of 494,260 cases of acute diarrhoea in the target population in the first five years following introduction. Given an estimate of 1.3 episodes per infant/child (based on CSD data), these episodes were estimated to affect a total of 379,665 children (75,933 per annum). The company expects a gradual uptake of racecadotril over the first five years, with a market share starting from 0.5% in year one and rising to 39.8% in year five.

5.1.2 Results

The company estimates the total net cost of using racecadotril plus ORS to be £7,236 in year one rising to £576,019 in year five. The results are summarised in Table 4 below. The company also explored the impact of variation of patient numbers treated in the range ± 25%. Estimated total costs ranged from £5,427 to £9,042 in year one to £432,014 to £720,023 in year five.

Table 4 Company-reported costs associated with the use of racecadotril (Hidrasec®) for the treatment of acute diarrhoea

	Year 1 (2012)	Year 2 (2013)	Year 3 (2014)	Year 4 (2015)	Year 5 (2016)
Number of eligible patients	75,933	75,933	75,933	75,933	75,933
Uptake (%)	0.50%	11.60%	24.50%	31.70%	39.80%
Treated patients	380	8,808	18,604	24,071	30,221
Net costs per patient					
Medication costs	£7,236	£167,885	£354,584	£458,789	£576,019
Primary care	-	-	-	-	-
Secondary & tertiary care	-	-	-	-	-
Staffing	-	-	-	-	-
Infrastructure	-	-	-	-	-
Personal social services	-	-	-	-	-
Overall net cost	£7,236	£167,885	£354,584	£458,789	£576,019

5.1.3 AWTTC critique

- The budget impact analysis presented by the company assumes all children with watery diarrhoea would be potentially eligible for treatment with racecadotril, rather than those meeting the licensed indication (those in whom ORS alone is insufficient).
- The analysis implicitly assumes no displacement of alternative symptomatic treatments (e.g. loperamide), and so would appear to reflect cases where loperamide is not a treatment option.
- CSD data used to estimate eligible patient numbers may not reflect actual incidence across Wales, being based on a sample of practices from 2010. Calculations are also based on constant incidence over the next five years. Any increase in incidence at a local level may skew estimates.
- The market share estimates used in the calculation are based on the company's projections and are expected to be subject to uncertainty.
- Collectively, the company's budget impact analyses appear subject to uncertainty.

5.2 Table of comparative unit costs

Table 5 provides example comparative costs for acute diarrhoea treatments licensed or used in infants and children under 12 years of age. Each would be given in addition to ORS, which when used at an example frequency of three times daily would have an acquisition cost of £0.75 to £1.00 per day, depending on brand used[17].

Table 5. Examples of costs of acute diarrhoea treatments in infants and children aged 3 months to 12 years used as add-on to oral rehydration solution therapy (ORS)

Treatment	Dose†	Approximate cost per day (in addition to ORS cost)
Racecadotril (Hidrasec®) infant 10 mg granules for oral suspension[3] **Racecadotril (Hidrasec®) children** 30 mg granules for oral suspension[2]	1.5 mg/kg three times daily. Equivalent to: ○ one 10mg sachet 3 times daily in infants less than 9kg; ○ two 10mg sachets 3 times daily for infants and children > 9kg; ○ one 30mg sachet 3 times daily for children weighing 13–27 kg; ○ two 30mg sachets 3 times daily for children > 27 kg.	**£1.26 to £2.52**
Loperamide hydrochloride (Imodium®) Oral, syrup 1 mg/5ml[26]	Under 4 years: not recommended 4–8 years: 1 mg 3–4 times daily for up to 3 days only 8–12 years: 2 mg 4 times daily for up to 5 days	**£0.18 to £0.47**
Loperamide hydrochloride (Non-proprietary) Oral, 2mg capsules[27]	Child 8–12 years: 2 mg 4 times daily for up to 5 days	**£0.13**
Co-phenotrope (Non-proprietary) Oral, tablets co-phenotrope 2.5/0.025[28] (diphenoxylate hydrochloride 2.5 mg, atropine sulfate 25 micrograms)	Child 2–4 years: half tablet 3 times daily Child 4–9 years: 1 tablet 3 times daily Child 9–12 years: 1 tablet 4 times daily	**£0.13 to £0.36**
Costs of comparators based on BNF list prices as of 15 October 2012[17]. †Based on BNF dosing instructions[17] and racecadotril SPC[2,3] This table does not imply therapeutic equivalence of the stated medicines and doses. See all relevant SPCs for full dosing details[2,3,26–28].		

6.0 ADDITIONAL INFORMATION

6.1 Appropriate place for prescribing

AWTTC is of the opinion that, if recommended, racecadotril (Hidrasec®) may be appropriate for prescribing by all prescribers within NHS Wales for the indication under consideration.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months[1].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

6.4 Evidence search
Date of evidence search: 1 October 2012
Date range of evidence search: No date limits were applied to database searches.

REFERENCES

1 Abbott Healthcare Products Ltd. Form B: detailed appraisal submission. Racecadotril (Hidrasec®▼). Sep 2012.

2 Abbott Healthcare Products Ltd. Hidrasec®▼ children 30 mg granules for oral suspension. Summary of Product Characteristics. Oct 2012. Available at: http://www.medicines.org.uk/EMC/medicine/27108/SPC/Hidrasec+children+30mg+granules+for+oral+suspension/. Accessed Oct 2012.

3 Abbott Healthcare Products Ltd. Hidrasec®▼ infant 10 mg granules for oral suspension. Summary of Product Characteristics. Oct 2012. Available at: http://www.medicines.org.uk/EMC/medicine/27109/SPC/Hidrasec+Infant+10mg+granules+for+oral+suspension/. Accessed Oct 2012.

4 Medicines and Healthcare products Regulatory Agency. Marketing authorisations granted in September 2011. 2012. Available at: http://www.mhra.gov.uk/home/groups/l-reg/documents/licensing/con134790.pdf. Accessed Oct 2012.

5 National Health Service Direct Wales. Gastroenteritis in children. 2012. Available at: http://www.nhsdirect.wales.nhs.uk/encyclopaedia/g/article/gastroenteritisinchildren/. Accessed Oct 2012.

6 World Gastroenterology Organisation Global Guidelines. Acute diarrhea in adults and children: a global perspective. Feb 2012. Available at: http://www.worldgastroenterology.org/assets/export/userfiles/Acute%20Diarrhea_long_FINAL_120604.pdf. Accessed Oct 2012.

7 National Institute for Health and Clinical Excellence. Clinical Guideline 84. Diarrhoea and vomiting in children under five: full guideline. Apr 2009. Available at: http://guidance.nice.org.uk/CG84/Guidance/pdf/English. Accessed Oct 2012.

8 National Institute for Health Research Horizon Scanning Centre. Racecadotril (Hidrasec®▼) for acute diarrhoea. Jun 2012. Available at: http://www.hsc.nihr.ac.uk/topics/racecadotril-for-acute-diarrhoea-infants-older-tha/. Accessed Oct 2012.

9 British Medical Association, Royal Pharmaceutical Society of Great Britain. *British National Formulary for Children 2012—2013.* Jan 2012.

10 Abbott Healthcare Products Ltd. Hidrasec®▼ 100 mg hard capsules. Summary of Product Characteristics. Oct 2012. Available at: http://www.medicines.org.uk/EMC/medicine/27107/SPC/Hidrasec+100mg+Hard+capsules/. Accessed Nov 2012.

11 All Wales Medicines Strategy Group. Statement of Advice: Racecadotril (Hidrasec®▼) capsules Symptomatic treatment of acute diarrhoea in adults. Bioproject Pharma Ltd. Mar 2012. Available at: http://www.wales.nhs.uk/sites3/Documents/371/Statement%20of%20Advice%20Hidrasec%20capsules.pdf. Accessed Nov 2012.

12 Lehert P, Cheron G, Alvarez Calatayud G et al. Racecadotril for childhood gastroenteritis: an individual patient data meta-analysis. *Digestive and Liver Disease* 2011; 43 (9): 707-13.

13 Santos M, Maranon R, Miguez C. Use of racecadotril as outpatient treatment for acute gastroenteritis: a prospective, randomized, parallel study. *J Paediatr* 2009; 155: 62-7.

14 Cézard JP, Duhamel JF, Meyer M et al. Efficacy and Tolerability of Racecadotril in Acute Diarrhea in Children. *Gastroenterology* 2001; 120: 799-805.

15 Salazar-Lindo E, Santisteban-Ponce J, Chea-Woo E et al. Racecadotril in the treatment of acute watery diarrhea in children. *New England Journal of Medecine* 2011; 463-7.

16 Álvarez Calatayud G, Simon G, Taboada Castro L et al. The effectiveness of racecadotril in the treatment of acute gastroenteritis. *Act Pediatr Esp* 2009; 67 (3): 117-22.
17 British Medical Association, Royal Pharmaceutical Society of Great Britain. *British National Formulary. No. 64.* Oct 2012.
18 Chacon J. Analysis of factors influencing the overall effect of racecadotril on childhood acute diarrhea. Results from a real-world and post-authorization surveillance study in Venezuela. *Therapeutics and clinical risk management* 2010; 6: 293-9.
19 Turck D, Berard H, Fretault N et al. Comparison of racecadotril and loperamide in children with acute diarrhoea. *Aliment Pharmacol Ther* 1999; 13 (6): 27-32.
20 Cojocaru B, Bocquet N, Timsit et al. Effect of racecadotril in the management of acute diarrhoea in infants and children. *Arch Pediatr* 2002; 9 (8): 774-9.
21 Cegedim Strategic Data UK Ltd. Number of reconsultations. 2011.
22 Martin A, Cottrell S, Standaert B. Estimating utility scores in young children with acute rotavirus gastroenteritis in the UK. *J Med Econ* 2008; 11 (3): 471-8.
23 Personal Social Services Research Unit. Unit costs of health and social care. 2010. Available at: http://www.pssru.ac.uk/project-pages/unit-costs/2010/index.php. Accessed Nov 2012.
24 Information Services Division Scotland. Speciality costs and activity - inpatients in all specialities (exc long stay), by patient type, by board. Mar 2011. Available at: http://www.isdscotland.org/Health-Topics/Finance/Costs/Detailed-Tables/Speciality-Costs/Acute-Medical.asp. Accessed Nov 2012.
25 Rautenberg TA, Zerwes U, Foester D et al. Evaluating the cost utility of racecadotril for the treatment of acute watery diarrhea in children: the RAWD model. *Clinicoecon Outcomes Res* 2012; 4: 109-16.
26 Janssen-Cilag Ltd. Imodium Syrup®. Summary of Product Characteristics. Sep 2012. Available at: http://www.medicines.org.uk/EMC/medicine/17607/SPC/Imodium+Syrup/. Accessed Nov 2012.
27 The Boots Company PLC. Boots Diarrhoea Relief 2 mg capsules (GSL and P). Summary of Product Characteristics. Nov 2011. Available at: http://www.medicines.org.uk/EMC/medicine/11642/SPC/Boots+Diarrhoea+Relief++2+mg+Capsules+(GSL+and+P)/. Accessed Nov 2012.
28 Mercury Pharma Group. Co-phenotrope 2.5/0.025 tablets. Summary of Product Characteristics. Nov 2011. Accessed Nov 2012.
29 Savitha MR, Mysore GML. Racecadotril - a novel drug for treatment of acute watery diarrhoea in Indian children. Presented at Karnataka Pedicon 2005.

Appendix 1. Additional clinical information.

Table 1A. Randomised controlled trials investigating racecadotril in infants and children with acute diarrhoea[1].

Study author	Patient number	Country	Study design and setting	Patient age	Primary outcome	Treatment regimens	Results[†]	
Cézard 2001[14]	168	France	Placebo controlled, inpatient	3–48 months	Stool output (g/Kg body weight) during 48 hours	Racecadotril + ORS	26.3 ± 3.8 g	p = 0.009
						Placebo + ORS	72.4 ± 10.7 g	
Salazar- Lindo 2000[15]*	135	Peru	Placebo controlled, inpatient	3–35 months	Stool output (g/Kg body weight) during 48 hours	Racecadotril + ORS	92.2 ± 97.2 g	p < 0.001
						Placebo + ORS	169.6 ± 124.5 g	
Cojocaru 2002[20]	164	France	Open label, outpatient	3–36 months	Number of additional consultations in week following admission to emergency department	Racecadotril + rehydration therapy (RT)	14/76	p < 0.05
						RT alone	27/78	
Álvarez-Calatayud 2009[16]	148	Spain	Cohort, outpatient	3–36 months	Number of diarrhoeic stools after 48 hours	Racecadotril + ORS	40.7% of patients	p < 0.0001
						ORS alone	77.9% of patients	
Santos 2006[13]	179	Spain	Open label, outpatient	3–36 months	Total number of diarrhoeic stools within 48 hours of treatment	Racecadotril + ORS	3.8 ± 2.4	Difference not statistically significant
						ORS alone	4.1 ± 2.7	
Gutierrez-Castrellon 2008[1]*	270	Mexico	Placebo controlled, inpatient	1–24 months	Stool output after 48 hours	Racecadotril + ORS	102 ± 18 g	p < 0.01
						Placebo + ORS	189 ± 34 g	
Gutierrez-Castrellon 2008[1]	184	Mexico	Placebo controlled, outpatient	1–60 months	Number of diarrhoeic stools during 48 hours	Racecadotril + ORS	5.6 ± 1.7	p < 0.01
						Placebo + ORS	11.3 ± 2.7	
Savitha 2005[29]	60	India	Placebo controlled, inpatient	3–60 months	Mean diarrhoea duration	Racecadotril + ORS	40.0 hours	p < 0.01
						Placebo + ORS	61.6 hours	
Melendez Garcia 2007[1]	50	Guatemala	Outpatient	3–71 months	Total number of diarrhoeic stools	Racecadotril + ORS	Results not reported in Lehert et al (2011)[12]	
						Placebo + ORS		

ORS: oral rehydration solution; *Female patients were excluded in the Salazar-Lindo et al[15] and the Gutierrez-Castrellon[1] et al inpatient trial. [†]All figures reported as ± standard deviation except for Cezard 2001 (standard error of the mean), Salazar-Lindo 2000 (standard error), Álvarez- Calatayud 2009 (not specified) and Savitha 2005 (not specified).
Dosing of racecadotril was in line with the summaries of product characteristics (SPCs) for the Cézard et al[14], Salazar-Lindo et al[15] , Cojocaru et al[20] , Santos et al[13] and the two Gutierrez-Castrellon et al[1] trials. The Álvarez-Calatayud et al[16] trial used a dose of 30 mg three times daily for children weighing > 9 Kg, whilst the SPC recommends two 10 mg sachets three times daily for children weighing between 9 Kg and 13 Kg[2,3]. Dose information was not available for the remaining trials.