



Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

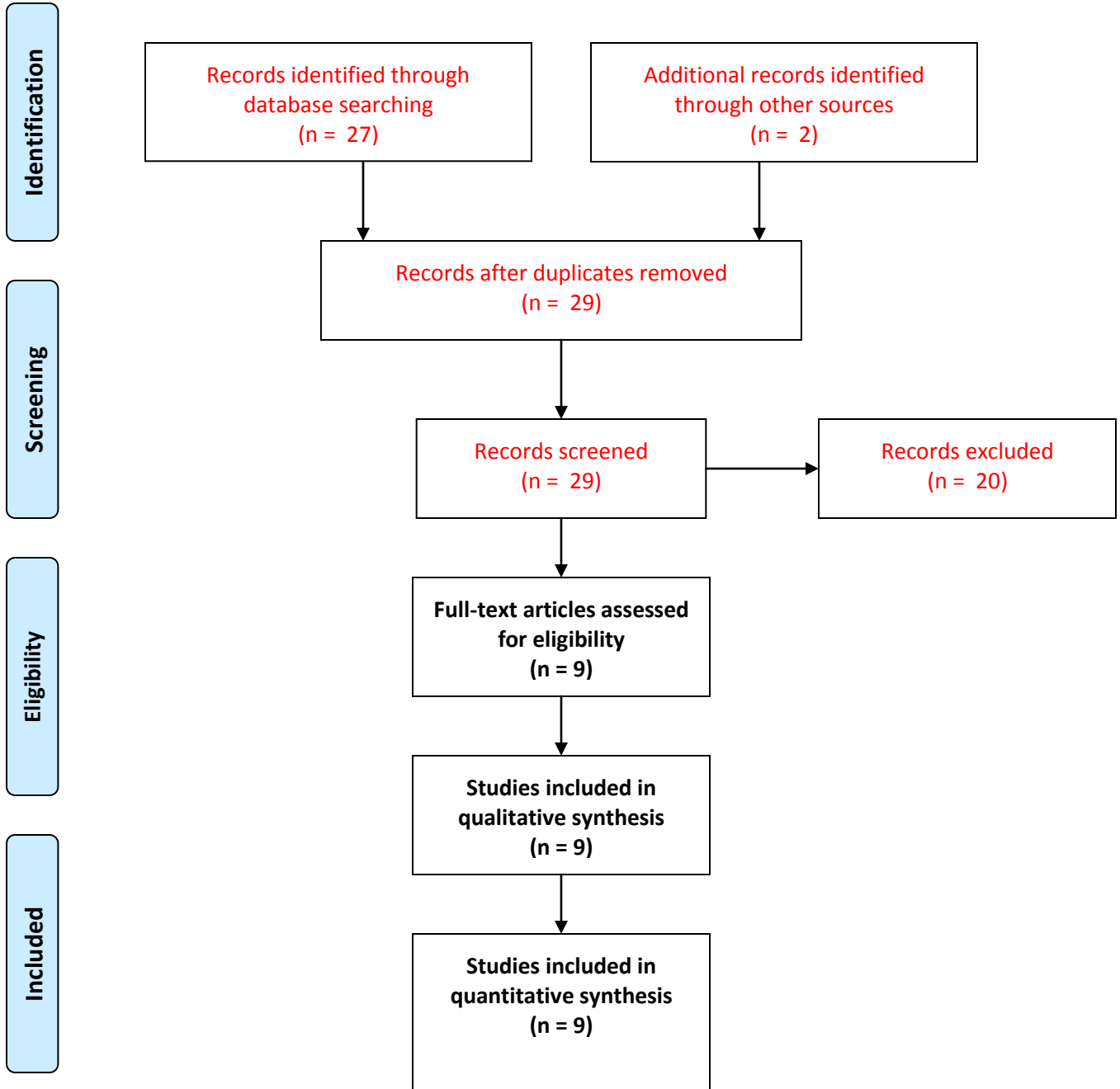
Name of medicine (INN): Racecadotril 100 mg capsule, 10 mg and 30 mg sachet oral powder	
Indication:	<ul style="list-style-type: none">• 100 mg capsule : for the treatment of acute diarrhea• 10 mg sachet , 30 mg sachet oral powder: adjunct to oral or parenteral rehydration in the treatment of acute watery diarrhea in children
Date of deliberation:	24 July 2015 26 November 2015
Recommendation:	DISAPPROVAL
Clinical evidence:	<p>The Council recognized that in a meta-analysis among children with acute gastroenteritis, racecadotril resulted in better control in terms of reducing the duration to less than 2 days (RR= 1.98; 95%CI: 1.71 and 2.28). Likewise, the duration of diarrhea with racecadotril was shorter compared to ORS alone (1.75 days vs. 2.17 days) (Lehert et al, 2011). Among adults, racecadotril also decreased the diarrhea episodes during the first day of treatment (4.3 vs. 5.4; p=0.02) (Hamza et al, 1999) and when compared with loperamide, it provided better effectiveness among elderly with fewer diarrhea episodes (3.93 vs. 7.29; p<0.01) (Gallelli et al. 2010). However, the difference was not significant among younger adults. With regard to the treatment of cholera, racecadotril does not provide additional benefit.</p> <p>In terms of safety, racecadotril has lower incidence of adverse events like dizziness or malaise when compared with ORS (3.1% vs. 5.3%; Hamza et al. 1999) or nausea and constipation when compared with loperamide (14.2% vs. 23.9%; p=0.001; Pradoi et al. 2002) respectively.</p> <p><i>(See Attachment for the full ERG evaluation)</i></p>
Cost data:	<p>The direct costs of treatment with racecadotril as an adjunct to ORS are Php 232.60 for adults and Php 271.32 for children. These are twice as high as the cost of treatment for ORS alone, i.e., Php 119 (adults) and Php 144 (children).</p> <p><i>(See Attachment).</i></p>

Remarks:

The Council noted that the benefits of racecadotril over ORS are statistically but not clinically significant. Likewise, the proposed medicine is not included in the evidence based guidelines for diarrhea. Thus, the recommendation of the Council to disapprove its inclusion still remains.

The Secretary of Health has officially disapproved the proposal to include racecadotril in the PNF.

PRISMA Table



1. Among children and adults with acute diarrhea, would racecadotril and ORS vs. ORS alone shorten the course of the diarrhea?

EVIDENCE TABLE 1

NO	TITLE/ AUTHOR YEAR/JOURNAL	STUDY DESIGN	PARTICIPANT DESCRIPTION	INTERVENTION	RESULTS/OUTCOMES					GRADE OF EVIDENCE	REMARKS
					EVENTS (including adverse events)	Racecadotril		Control			
						No. of events *	Total # of patients	No. of events *	Total # of patients		
1	Lehert et al. Digest Liver Dis, 2011	Meta-analysis	9 RCTs on children with acute gastroenteritis	Racecadotril vs. control	Responders (less than 2 days diarrhea after treatment)	352	692	168	692	High	RR=1.98; 95%CI: 1.71 and 2.28
					Diarrhea duration	1.75 days		2.17 days			
	Hao, R et al, PIDSP Journal, 2010	Meta-analysis	4 RCTs with 659 participants on children with acute gastroenteritis	Racecadotril plus ORS vs. ORS plus placebo	cure rates in 7 days (reported here are the non-responders)	37	207	60	203	High	RR=0.62 (95% CI 0.43,0.88)
					duration of diarrhea in days						Mean Difference =-0.63 (95% CI -0.85, -0.41)
					adverse events	44	332	44	327		NS
2	Gallelli et al. Eur J Clin Pharmacol. 2010	RCT	61 elderly patients with acute diarrhea	Racecadotril plus ORS vs. loperamide plus ORS	Diarrhea episodes	3.93	SD 2.99	7.29	SD 4.45	High	p=<0.01
					Duration of abdominal pain	14 hrs	SD 1 hr	32 hrs	SD 1 hr		
					Stool output	120 g/kg	SD 27	150 g/kg	SD 39		
					Adverse event (nausea, constipation)	12%		20%			
3	Hamza et al. Aliment Pharmacol Ther. 1999	RCT	70 adult patients with acute diarrhea	Racecadotril vs. placebo	Stool weight during 1 st day	355 gm	SD 35	499 gm	SD 46	High	p=0.027
					Diarrhea episodes 1 st day	4.3	SD 0.4	5.4	SD 0.4		

					Adverse event (dizziness, malaise)	3.1%	32	5.3%	38		
4	Alam et al. Gut, 2003	RCT, double blind	110 adult patients with cholera	Racecadotril plus WHO ORS vs. WHO ORS	Success rate	96%	54	89%	56	High	NS
					Duration of diarrhea	Kaplan-Mier curve		Kaplan-Mier curve			Similar between groups
5	Prado. Scand J Gastroenterol 2002	RCT	945 adult patients with acute diarrhea	Racecadotril vs. loperamide	Diarrhea duration	55 hrs	50-65	55	48-66	High	
					Clinical success	92%	473	93%	471		
					Duration of abdominal pain	11 hrs		10 hrs			
					Adverse events	67 (14.2%)	473	113 (23.9%)	471		
6	Vetel et al. Aliment Pharmacol Ther	RCT	157 adults with acute diarrhea	Racecadotril vs. loperamide	Diarrhea episodes	3.5	SD 0.5	2.9	SD 0.4	High	NS
					Duration of diarrhea	14.9 hrs	SD 2	13.7 hrs	SD 2.2		NS
7	Wang et al. World J Gastroenterol 2005	RCT	62 adult patients with acute diarrhea	Racecadotril vs. loperamide	Diarrhea duration	19.5 hrs		13 hrs		High	NS
					Clinical success	87.1%		87.1%			NS
					Adverse event (constipation, itching)	25%		22%			NS
	Rautenberg, TA et al, Clinicoecon Outcomes Res, 2012	Cost-utility		Racecadotril plus ORS vs. ORS alone	Drug Cost	£12.17		£3.03		High	total incremental cost minus £ 379 in favor of racecadotril
					Primary Care Cost	£51.12		£62.64			
					Secondary Care Cost	£40.20		£416.82			
					Adverse Events Cost	£0.35		£0.46			
					Total Cost	£103.84		£482.95			

EVIDENCE TABLE 2: GRADE EVIDENCE PROFILE TABLE

QUALITY ASSESSMENT							SUMMARY OF FINDINGS				Over-all Quality	Importance
							No. of patients		Effect			
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute MD		
Outcome: Responders in 2 days for diarrhea in children												
1	Meta-analyses	None	None	None	None		Racecadotril plus ORS	ORS	1.98; 95%CI: 1.71 and 2.28		High	Critical
Outcome: Non-response in 7 days for diarrhea in children												
1	Meta-analyses	None	None	None	None		Racecadotril plus ORS	ORS	0.62 (95% CI 0.43,0.88)		High	Critical

DETAILS REQUIRED FOR COST-EFFECTIVENESS ANALYSIS

<p align="center">PARAMETER (Indicate information for intended recipient)* <i><u>INTENDED RECIPIENT:</u></i></p>	<p align="center">NEW MEDICINE OR PROPOSED NEW INDICATION/ FORMULATION/ ROUTE OF ADMINISTRATION</p>	<p align="center">CURRENTLY LISTED MEDICINE FOR SAME INDICATION IN THE PNF</p>	<p align="center">REFERENCES</p>
<p>COST PER DOSAGE UNIT (in PhP)</p> <p>a. Proposed list price to the government</p> <p>b. Current prevailing market price</p>	<p align="center"><u>Adult</u> ¹Racecadotril 100mg (Hidrasec) Php 28.10/tab</p> <p align="center"><u>Children</u> ¹Racecadotril 30mg powder (Hidrasec) Php 29.22/pack</p>	<p align="center"><u>Adult</u> ²ORS Php 8.00/sachet</p> <p align="center">²Loperamide Php 1.00</p> <p align="center"><u>Children</u> ²ORS Php 8.00/sachet</p>	<p align="center">¹MIMS ²DPRI</p>
<p>NUMBER OF DOSAGE UNITS PER UNIT COURSE</p>	<p align="center">Adults 6 (100 mg tabs) 3 daily doses for 2 days</p> <p align="center">8 ORS pack considering 4 diarrheal episodes (Gallelli et al, 2010)</p> <p align="center">Children 6 (30mg pack) 12 ORS pack</p>	<p align="center">Adult 7 loperamide tabs considering 7 diarrheal episodes</p> <p align="center">14 ORS pack considering 7 diarrheal episodes (Gallelli et al, 2010)</p> <p align="center">Children 18 ORS pack</p>	<p align="center">Based on diarrhea duration of 2 days for racecadotril and 3 days for ORS</p>
<p>TOTAL DIRECT COST PER PATIENT PER TREATMENT COURSE (in PhP)</p>	<p align="center">Adult Php 232.60</p> <p align="center">Children Php 271.32</p>	<p align="center">Adult Php 119</p> <p align="center">Children Php 144</p>	
<p>ADDITIONAL COST PER PATIENT PER TREATMENT COURSE: (n PhP)</p> <p>a. Direct cost of hospital stay</p> <p>b. Indirect cost (lost day from work)</p>			
<p>TOTAL COST PER PATIENT PER TREATMENT COURSE (in PhP) Total Direct + Additional Costs</p>	<p align="center">Adult Php 232.60</p> <p align="center">Children Php 271.32</p>	<p align="center">Adult Php 119</p> <p align="center">Children Php 144</p>	

ESTIMATED NUMBER OF PATIENTS WITH THE DISEASE/CONDITION WHO WILL USE THE MEDICINE			
QUALITY ADJUSTED LIFE YEARS (IF AVAILABLE)	+0.0008 for a 6 day period		favours racecadotril with ORS over ORS alone for details and costing see evidence table on the study of Rautenberg et al, 2012
DISABILITY ADJUSTED LIFE YEARS (IF AVAILABLE)			

REVIEWERS' RECOMMENDATIONS

Literature Search

- We search Pubmed last April 2015 using the term “racecadotril” and limit to meta-analysis articles. This yielded only 1 article published in 2011 which is a meta-analysis among children with diarrheas. We then updated the search to “racecadotril” and limit to randomized controlled trials in adults and children. This yielded 26 articles.
- We reviewed the 27 articles and considered 9 articles for full text retrieval. We reviewed the 9 articles and included all 9 in this review.
 - Leherth P(1), Chéron G, Calatayud GA, Cézard JP, Castrellón PG, Garcia JM, Santos M, Savitha MR. Racecadotril for childhood gastroenteritis: an individual patient data meta-analysis. *Dig Liver Dis.* 2011 Sep;43(9):707-13. doi: 10.1016/j.dld.2011.03.001. Epub 2011 Apr 22.
 - Hao R (1), De Vera M, Resurrecion E. Racecadotril in the Treatment of Acute Diarrhea in children: A Meta-Analysis. *PIDSP Journal July-Dec;11(2):19-32*
 - Rautenberg TA(1), Zerwes U, Foerster D, Aultman R. Evaluating the cost utility of racecadotril for the treatment of acute watery diarrhea in children: the RAWD mode. *Clinicoecon Outcomes Res.* 2012; 4: 109–116. Epub 2012 Apr. 20.
 - Gallelli L(1), Colosimo M, Tolotta GA, Falcone D, Luberto L, Curto LS, Rende P, Mazzei F, Marigliano NM, De Sarro G, Cucchiara S. Prospective randomized double-blind trial of racecadotril compared with loperamide in elderly people with gastroenteritis living in nursing homes. *Eur J Clin Pharmacol.* 2010 Feb;66(2):137-44. doi: 10.1007/s00228-009-0751-3. Epub 2009 Nov 10.
 - Wang HH(1), Shieh MJ, Liao KF. A blind, randomized comparison of racecadotril and loperamide for stopping acute diarrhea in adults. *World J Gastroenterol.* 2005 Mar 14;11(10):1540-3.
 - Alam NH(1), Ashraf H, Khan WA, Karim MM, Fuchs GJ. Efficacy and tolerability of racecadotril in the treatment of cholera in adults: a double blind, randomised, controlled clinical trial. *Gut.* 2003 Oct;52(10):1419-23.
 - Prado D(1); Global Adult Racecadotril Study Group. A multinational comparison of racecadotril and loperamide in the treatment of acute watery diarrhoea in adults. *Scand J Gastroenterol.* 2002 Jun;37(6):656-61.
 - Vetel JM(1), Berard H, Fretault N, Lecomte JM. Comparison of racecadotril and loperamide in adults with acute diarrhoea. *Aliment Pharmacol Ther.* 1999 Dec;13 Suppl 6:21-6.
 - Hamza H(1), Ben Khalifa H, Baumer P, Berard H, Lecomte JM. Racecadotril versus placebo in the treatment of acute diarrhoea in adults. *Aliment Pharmacol Ther.* 1999 Dec;13 Suppl 6:15-9.

Effectiveness/Efficacy

- In a meta-analysis among children with acute gastroenteritis, racecadotril resulted to better control of diarrhea in less than 2 days (RR= 1.98; 95%CI: 1.71 and 2.28). The duration of diarrhea with racecadotril was shorter compared to ORS alone (1.75 days vs. 2.17 days) (Leherth et al, 2011).
- Among adults, racecadotril also decreased the diarrhea episodes during the first day of treatment (4.3 vs. 5.4; p=0.02)(Hamza et al, 1999).
- When compared with loperamide, racecadotril provided better effectiveness among elderly with fewer diarrhea episodes (3.93 vs. 7.29; p<0.01)(Gallelli et al. 2010). But the difference was not significant among younger adults.
- Racecadotril has no significant additional benefit for the treatment of cholera.

Safety

- In terms of safety, racecadotril has lower adverse event like dizziness or malaise when compared with ORS (3.1% vs. 5.3%; Hamza et al. 1999) or nausea and constipation when compared with loperamide (14.2% vs. 23.9%; Pradoi et al. 2002) respectively.

Summary of Review

- Overall we found racecadotril to shorten the duration of diarrhea among children and adults. It also has better safety profile than loperamide.

Cost Data

- The direct costs of treatment with racecadotril as an adjunct to ORS are Php 232.60 for adults and Php 271.32 for children. These are twice as high as the cost of treatment for ORS alone, i.e., Php 119 (adults) and Php 144 (children).
- The study of Rautenberg et al, 2012 showed a deterministic cost comparison which pegs expenses for ORS alone at £482.95 (P 33,181.83) compared with racecadotril + ORS at £103.84 (P 7134.51)

Overall Recommendation

- Overall, racecadotril shorten the duration of diarrhea among children and adult and has better safety profile than loperamide. It is also more cost-effective when indirect costs of treatment were also considered.
- There is enough evidence and justification to recommend the inclusion of racecadotril in the formulary.

References

1. Leher P(1), Chéron G, Calatayud GA, Cézard JP, Castrellón PG, Garcia JM, Santos M, Savitha MR. Racecadotril for childhood gastroenteritis: an individual patient data meta-analysis. *Dig Liver Dis.* 2011 Sep;43(9):707-13. doi: 10.1016/j.dld.2011.03.001. Epub 2011 Apr 22.
2. Gallelli L(1), Colosimo M, Tolotta GA, Falcone D, Luberto L, Curto LS, Rende P, Mazzei F, Marigliano NM, De Sarro G, Cucchiara S. Prospective randomized double-blind trial of racecadotril compared with loperamide in elderly people with gastroenteritis living in nursing homes. *Eur J Clin Pharmacol.* 2010 Feb;66(2):137-44. doi: 10.1007/s00228-009-0751-3. Epub 2009 Nov 10.
3. Wang HH(1), Shieh MJ, Liao KF. A blind, randomized comparison of racecadotril and loperamide for stopping acute diarrhea in adults. *World J Gastroenterol.* 2005 Mar 14;11(10):1540-3.
4. Alam NH(1), Ashraf H, Khan WA, Karim MM, Fuchs GJ. Efficacy and tolerability of racecadotril in the treatment of cholera in adults: a double blind, randomised, controlled clinical trial. *Gut.* 2003 Oct;52(10):1419-23.
5. Prado D(1); Global Adult Racecadotril Study Group. A multinational comparison of racecadotril and loperamide in the treatment of acute watery diarrhoea in adults. *Scand J Gastroenterol.* 2002 Jun;37(6):656-61.
6. Vetel JM(1), Berard H, Fretault N, Lecomte JM. Comparison of racecadotril and loperamide in adults with acute diarrhoea. *Aliment Pharmacol Ther.* 1999 Dec;13 Suppl 6:21-6.

7. Hamza H(1), Ben Khalifa H, Baumer P, Berard H, Lecomte JM. Racecadotril versus placebo in the treatment of acute diarrhoea in adults. *Aliment Pharmacol Ther.* 1999 Dec;13 Suppl 6:15-9.
8. Hao R (1), De Vera M, Resurrecion E. Racecadotril in the Treatment of Acute Diarrhea in children: A Meta-Analysis. *PIDSP Journal* July-Dec;11(2):19-32
9. Rautenberg TA(1), Zerwes U, Foerster D, Aultman R. Evaluating the cost utility of racecadotril for the treatment of acute watery diarrhea in children: the RAWD mode. *Clinicoecon Outcomes Res.* 2012; 4: 109–116. Epub 2012 Apr. 20.

Response to appeal on the reviewers' recommendation on Racecadotril

We reviewed the appeal on racecadotril. We found out that the decision of the FEC was based on direct cost issue despite the favorable recommendation by the ERG.

Because cost is significant issue for PNF, it is recommended that the manufacturer decrease the cost of racecadotril comparable to current drugs in the PNF for diarrhea.