PROPOSAL FOR THE INCLUSION OF RACECADOTRIL IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES

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1. Summary statement of the proposal for inclusion, change or deletion

Researcher Alan Lopez, PhD, and colleagues combed through thousands of data sources from all over the globe on 136 diseases and injuries in 2001.
Lopez works in Brisbane, Australia at the University of Queensland's School of Population Health. He and his colleagues published the results in *The Lancet*. Among their findings:
Slightly more than 56 million people died in 2001.
Those deaths included 10.6 million children, almost all of whom (99%) lived in low- and middle-income countries.
More than half of the children died from 5 preventable or treatable conditions:
- Respiratory infections
- Measles
- **Diarrhea**
- Malaria
- HIV/AIDS

The mortality rate for children under the age of 5 caused by acute diarrhea is estimated by WHO at 1.8 Million deaths annually.

To limit and to offset the losses of water and electrolytes are key measures in the treatment of acute diarrhea for children, in particular for the most exposed population: children under the age of 3 years.
Accordingly, this confirms WHO recommendation to use Oral Rehydratation Salts (ORS) for these cases and no other specific drug.
However when this recommendation was written the new class of antisecretory agents could not be considered since it was written before the discovery of the first entry in this class: Racecadotril.

Nevertheless, Racecadotril is extremely well positioned in the guidelines of WHO: it is the only medicine which has a proven efficacy in reducing water and electrolyte losses measured by the only criteria recognized by WHO: the stool output.
This efficacy has been proven in two randomized double blind clinical trials: placebo + ORS vs. Racecadotril + ORS which have been published in the two following scientific magazines:

- **Gastroenterology** 2001; 120 :799-805 for following study: *Cézard JP, et al., efficacy and tolerability of Racecadotril in acute diarrhea in children.*

- **New England Journal of Medicine** 2000; 343:463-7 for following study: *Salazar-Lindo E, et al., Racecadotril in the treatment of acute watery diarrhea in children.*

Therefore the action of Racecadotril is supplementary to the rehydration and improves the compliance of the use of ORS.
It reduces also the need for future care with less intravenous rehydration and less secondary consultation (*Cojocaru, et al., Effect of Racecadotril in acute diarrhea in infants and children Arch Pediatr (Paris) 2002;8:774-9 (trial not sponsored by Bioprojet*))
Racecadotril does not cause any complications such as the ones caused by other anti-diarrheal medications, as it does not slow the forward propulsion of intestinal contents and has no effect on the nervous system and no respiratory distress. Its excellent safety profile has been highlighted (i) during clinical trials whith side effects in line in frequency and in type with the ones of the placebo group (ii) in pharmacovigilance with an extremely low frequency of adverse events reported in infants and young children treated with 10mg Racecadotril (weight below 13 kg, then below 2 of age) : 1.68 AE’s per million, i.e. one adverse event for 600,000 treatments (data from Periodic Safety Update Report 2006).

Racecadotril complies with WHO guidelines as highlighted various international groups which update WHO recommendations, in particular following groups :
the French speaking group of Hepatology, Gastroenterology and Pediatric Nutrition : "***Racecadotril is the only drug which proved a significant reduction in stool output***" *(Cezard JP, et al., Treatment with medicines of infectious acute diarrhea in infants and children; Arch Pediatr (Paris) 2002;9 :620-8*)
the Canadian Paediatric Society: "***Racecadotril, an antisecretory agent, is safe and efficient and can be routinely used in acute watery diarrhea in addition to ORS.***" *(Canadian Paediatric Society. Treatment of diarrheal disease; Position statement; Paediatr Child health 2003;8:455-8 and 463-66).*

2. Name of the focal point in WHO submitting or supporting the application

3. Name of the organization(s) consulted and/or supporting the application

Pr. Eduardo SALAZAR-LINDO
WHO Expert
Department of Pediatrics, Cayetano Heredia Hospital, Lima, Peru

4. International Non-proprietary Name (INN, generic name) of the medicine

Racecadotril.

5. Formulation proposed for inclusion; including adult and paediatric (if appropriate)

Children of 3 months to 2 years of age: 16 sachets of 1g powder containing 10mg of Racecadotril

Children of 2 years to 15 years of age (approx.) : 16 or 30 sachets of 3g powder containing 30mg of Racecadotril

Adults : 9, 10 or 20 capsules containing 100 mg of Racecadotril

6. International availability - sources, if possible manufacturers (see also section 13)

Racecadotril Adult form was first launched in France in 1993.
The product is sold either under the Brand name TIORFAN® or under the name HIDRASEC®.
Racecadotril has been first launched in France in late 2000 **with a paediatric presentation** (in sachets). Furthermore it has been launched outside France only since 2004 (except for Spain in 2002)
Racecadotril is now approved and launched in 7 European countries: in addition to France and Spain, it is available in Germany, Portugal, Greece, Bulgaria and Romania. Thanks to a Mutual Recognition Procedure to be launched in the European Union on second half 2006, the rest of Europe should be covered before the end of this year.

It is available as well in Latin America.
In Asia the first registrations have just been obtained in the Philippines, Indonesia, Thailand and Vietnam and are still pending in most of the other asian countries. It is approved in Tunisia and Morocco, still pending in Algeria, Egypt and Lybia.
The files for registrations should be submitted shortly in the rest of Africa, in the Balkanic countries, in Russia and in the CIS.

The product has started to be more commonly available clearly **after the writing of WHO guidelines in 2003**. (*The Treatment of Diarrhea –A manual for physicians and other health workers: WHO/CAH/03.7).*

The products are today manufactured in France (Sophartex) and in Spain (Ferrer Grupo) in GMP approved facilities.

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Listing is requested as an individual medicine to be taken in addition of an Oral Rehydration Salt.

Racecadotril is the first intestinal antisecretory drug.

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment on current use, target population)

Diarrhea – morbidity is more than double in developing countries with
close to 4 diarrheal episodes per year with children under 5 years versus 1.8 in developed countries.

- 90% of globally 4 million diarrheal episodes occur in developing countries
- 8-14 episodes per year per child between 6-24 months*
- 5-8 episodes per year per child in total being younger than 5 years*

*Summary estimates for **morbidity** from diarrheal diseases*

	Diarrhoeal episodes (millions)		*Episodes of diarrhoea per person per year*	
Region	*All ages*	*< 5 years*	*All ages*	*< 5 years*
Established Market Economies	167.2	92.6	0.21	1.8
Former Socialist Economies of Europe	93.8	61.9	0.27	2.3
India	787.9	524.1	0.93	4.5
China	1010.3	318.2	0.89	2.3
Other Asia and Islands	496.7	301.0	0.73	4.0
Sub-Saharan Africa	653.1	444.4	1.28	5.0
Latin America and the Caribbean	434.5	225.6	0.98	4.0
Middle Eastern Crescent	430.3	307.7	0.86	4.0
World	4073.9	2275.4	0.77	3.6

* Data from Latin America, Africa, India (likely to be underestimated)
- Incidence rates likely to be the same in all developing countries

Diarrheal morbidity and mortality in 276 surveys in children younger than 5 years (WHO methodology, 1981–1986):

Region	Number of surveys	Number of countries	Episodes/child/year		Deaths per 1000 children per year		Diarrhoeal deaths as a percentage of total (median)
			Median	Range	Median	Range	
Latin America and Caribbean	12	8	4.9	0.8–10.4	4.2	1.2–9.2	35
Sub-Saharan Africa	67	22	4.4	1.6–9.9	10.6	3.1–54.9	38
Middle East and North Africa	47	10	2.7	2.1–10.8	5.8	1.0–25.3	39
Asia and the Pacific	150	20	2.6	1.1–5.7	3.2	0.0–17.2	29
India	—	1	2.7	—	3.2	—	—
China	—	1	1.2	—	0.0	—	—
Other	—	18	2.6	—	3.3	—	—
All regions	276	60	3.5	0.8–10.8	6.5	0.0–54.9	36

Diarrhea – estimates for episode distribution and type

Mortality of children especially high due to persistent diarrhea.
Although substantially lower than the estimated 5 million deaths per year worldwide 20 years ago, yet 1.5 to 2.5 million deaths occur every year among children younger than 5 years.

- Persistent and acute diarrhea are particularly associated with malnutrition
- Severe malnutrition seen as significant risk factor for mortality from acute, and even more from persistent diarrhea
- Pre existing malnutrition might lead to increased duration and severity of diarrhea
- Dysentery having more market effect on linear growth of the patient
- Median duration of watery diarrhea has been observed to be 4 to 5 days, while dysentery lasts longer to about 6 to11 days

Estimates for distribution of diarrheal episodes by type according to age

Age (years)	Percentage of episodes attributable to			Percentage of mortality attributable to		
	Watery diarrhoea	Persistent diarrhoea	Dysentery	Watery diarrhoea	Persistent diarrhoea	Dysentery
0–4	80	10	10	50	35	15
5–14	89	1	10	75	5	20
15–44	90	0	10	80	0	20
45–59	90	0	10	80	0	20
≥ 60	85	0	15	85	0	15

source:
Bern, 1992; Bhan et al 1986, Baqui et al. 1993; Black, Brown & Becker 1992

Cost Savings in Target Population

The cost of treatment is sizeable, but the cost associated with death due to diarrhea in the developing world is obviously greater.

Up to one third of paediatric hospital beds in endemic areas may be occupied by children with diarrhea.

Disease burden for hospitalizations associated with Rotavirus :

COUNTRY or REGION	Diarrhea as a discharge diagnosis	Annual rate of hospitalization	Cost of hospitalization
France (1997) *Arch Pediatr. 2003;10:861-8*	11%	1,385/100,000 child<5y	€ 62 millions/year
Sweden (1996) *Acta Paediatr. 1999;88:20-3*	2.3%	370/100,000 child<5y	USD 1.8-2 million/y
Hong-Kong (1988-98) *Epidemiol Infect 1998;120:321-5*	NR	200/100,000 child<5y	USD 1.2 million/y
New-York (1989-2000) *Pediatr Infect Dis J 2003;22:808-14*	13%	830/100,000 child<5y	NR
Spain (1999-2000) *Vaccine 2004;22:2221-5*	NR	100-250/100,000 child<5y	USD 3.6 million/y

COUNTRY or REGION	Annual rate of hospitalization	Diarrheal deaths
Argentina (1999) *Pediatr Infect Dis J 2002;21:843-50*	900/100,000 child<5y	16/100,000 child/year
Vietnam (1998-2000) *J Infect Dis 2001;183:1707-12*	NR	650/100,000 child/year
Bangladesh (1990-93) *Pediatr Infect Dis J 1997;16:947-51*	NR	495-900/100,000 child/year
Peru (1989-1996) *Pan Am J Public Health 2001;10:240-247*	500/100,000 child<5y	266/100,000 child/year

Estimated burden and medical costs of Rotavirus-associated diarrhea in Peru and USA :

Event per year	PERU (1)	USA (2) (3)
Episodes	384,000 (0.3 episodes /child /year)	2,700,000 (0.3 episodes /child /year)
Outpatient visits	64,000 (17% of episodes)	500,000 (19% of episodes)
Hospitals admissions	30,000 (47% of visits)	55,000 (11% of visits)
Deaths	1,600 (1 in 375 children)	negligible
Medical costs (USD)		
Total	2,600,000	274,000,000
Per visit	12	132
Per hospitalization	60	2,672

(1) Ehrenkranz et al. *Pan Am J Public Health 2001;10(4):240-247*
(2) Jin et al. *Pediatr Infect Dis 1996;15:397-404*
(3) Tucker et al. *Jama 1998 ;279(17) :1371-1376*

The use of cost-effective treatments like Racecadotril (coupled with ORS) can decrease this mortality and the costs associated with it, in particular the cost of secondary medical consultation as shown is section 12.

9. Treatment details

9.1 Indications for use

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The Racecadotril should be considered for all patients, including youngest children (from 1 month of age in France) with 2 exceptions:

- Renal or hepatic impairment, due to the absence of data in these populations

- Due to the presence of saccharose, as an excipient TIORFAN® (OR HIDRASEC®) INFANTS or CHILDREN is contraindicated in patients with fructose intolerance, glucose malabsorption syndrome and saccharase-isomaltase deficiency (Tiorfan and Hidrasec are the original trade names of the medicinal product containing Racecadotril),

9.2 Dosage regimens

TIORFAN®/HIDRASEC® INFANTS and TIORFAN®/HIDRASEC® CHILDREN are administered via the oral route together with oral rehydration.
The recommended dose is determined according to body weight: 1.5 mg/kg per administration, with an initial administration followed by 3 administrations in the course of the day.
There are no monitored clinical trials in infants under 3 months of age.

Active ingredients:

- For infants from 3 months to 2.5 years of age: Racecadotril sachets containing **10mg**

- For children from 2 years to approximately 15 years of age: Racecadotril sachets containing **30mg.**

Approximate number of sachets per administration according to the body weight of the child:

Age	Sachets per administration
From 3 to 9 months (less than 9 kg approx.)	1 sachet of 10 mg per administration
From 9 to 30 months (from 9 to 13 kg approx.)	2 sachets of 10 mg per administration
From 30 months to 9 years (from 13 to 27 kg approx.)	1 sachet of 30 mg per administration
Over 9 years (more than 27 kg approx.)	2 sachets of 30 mg per administration

The Adult presentation is then available for patients above approximately 15 years of age with capsules containing 100mg Racecadotril. The regimen is one capsule immediately and one capsule three times a day.

Administration is not recommended in patients with renal or liver failure.
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.

9.3 Duration of therapy

The duration of treatment in the clinical trials with children was 5 days. Treatment should be continued until two normal stools are recorded. Treatment should not exceed 7 days.

9.4 Reference to existing WHO and other clinical guidelines

Dehydration is the dominant risk to cope with in the management of acute diarrhea in young children, and the treatment of this risk has been dramatically improved since the use of ORS's (WHO, Geneva, 1990: *A manual for the treatment of diarrhea – for use by physicians and other senior health workers –WHO document WHO/CDD/SER/80.2 Rev. 2, 1990*). The reduction of the stool output is the corner stone of the symptomatic treatment of acute diarrhea with children either to prevent or to correct the dehydration.

The therapeutic management as recommended by WHO has not changed from 1995 to 2003 and is built on prevention and treatment of dehydration, with no place for any anti-diarrheal medication as stated in following recommendation: " *these agents though commonly used, have no practical benefit and are never indicated for the treatment of acute diarrhea in children. Some of them are dangerous" (i) WHO, Geneva, 1995: Division of Diarrheal and Acute Respiratory Disease Control: The treatment of Diarrhea, A manual for physicians and other senior health workers WHO/CDR/95.3 10/95. (ii) WHO, Geneva, 2003: The Treatment of Diarrhea –A manual for physicians and other health workers: WHO/CAH/03.7)*

It can be noted that the WHO analysis does not update the section related to anti-diarrheal medications: the products listed include following classes :

- *Adsorbents* (*e;g; kaolin, attapulgite, smectite, activated charcoal, cholestyramine).*
- *Antimotility drugs (e.g. loperamide hydrochloride, diphenoxylate with atropine, opiates and derivatives),*
- *Bismuth subsalycilate.*
- *Combinations of drugs.*

The class of intestinal antisecretory agents is not listed, simply because this new class was not available and widely spread when these guidelines were written by WHO.

As shown is section 6, The product has started to be more commonly available clearly **after the writing of WHO guidelines in 2003**. (*The Treatment of Diarrhea –A manual for physicians and other health workers: WHO/CAH/03.7).*
The need to have a medicine which could prevent from intestinal hypersecretion without slowing down the bowel movement is an old need. Accordingly, the perfect profile of such an antidiarrheal medicine was defined some 20 years ago (*Edelman R, Prevention and treatment of infectious diarrhea. Am J Med 1985;78:99-106*) as a product which could rapidly inhibit the intestinal hypersecretion without causing constipation and without any central effect. This perfect profile was again confirmed in the 90's : "*The perfect antidiarrheal drug should have a safe use thanks to a focused action purely on water and electrolytes movements, without any impact on the digestive motility*" (*Du Pont C, Benhamou PH. Treatment of acute diarrhea in children. In: Rambaud JC, Rampal P editors. Infectious acute diarrheas, Doin, Paris 1993: 157-169.*).

But this was only a wishful product until late 2000 when the first, and only one to date, product of this class has been launched in France with a paediatric presentation

Furthermore, *the drug Racecadotril meets the criteria set by WHO in 1990 to define the* efficacy of a drug that can be prescribed for acute diarrhea in children together with the rehydration salts: reduction of the duration of diarrhea and of the stool output with a proven lack of secondary effects."
Prescribing the Racecadotril together with the ORS is compliant with WHO guidelines as explained by Pr. Martinot (*Martinot A. Treatment of acute diarrhea in infants : practices still not in line with guidelines. Arch Pediatr (Paris) 2004;11: 895-97*) for the following two reasons:

(i) it reduces the dehydration risk: "*the only medicines recommended by WHO and considered as "antidiarrheal medicines" are the ones reducing the stool output by at least 30% compared to placebo and therefore reducing the dehydration risks. This is the case with Racecadotril, an antisecretory drug without any impact on the motility and which cuts by half the stool output.* "
(ii) One obstacle for a wider use of ORS is the following : ORS does not bring any **visible** effect in the diarrhea evolution. When the efficacy of Racecadotril can help to improve the observance of the use of ORS thanks to a "***prescription in association with* an antisecretory drug**" as proposed by Pr. Martinot (*Martinot A. Treatment of acute diarrhea in infants : practices still not in line with guidelines. Arch Pediatr (Paris) 2004;11: 895-97*).

Then Racecadotril prescription intensifies the use of ORS. This synergy has always been promoted by Bioprojet Pharma which also directly markets an ORS (**Fanolyte**®) in France and in Tunisia, compliant with WHO requirements.
Finally, what is the actual benefit of the association –ORS with Racecadotril-? Pr. Martinot and his team have just issued an article on the therapeutic management of infants'gastroenteritis: in the section "how to assess the therapeutic strategies'usefulness?", following observation is made : "*it is important to assess to what extent this reduction in stool output thanks to the use of Racecadotril practically helps in reducing the need for intraveneous rehydrations, the hospitalization rates or their respective durations, the secondary medical consultations*" (*Martinot A, Aurel M, Pruvost J, Hue V, Dubos F. Can the clinical epidemiology in emergency departments improve the therapeutic management in the infants' gostroenteritis cases? Arch Pediatr 2006;13: 553-9*).

The Cojocaru *et al.* independent study brought relevant answers to this need (see section 12.2)

This supports the most recent recommendations issued by various international Groups and Societies such as the ones listed in the Summary :
from the French speaking group of Hepatology, Gastroenterology and Paediatric Nutrition,
and from the Canadian Paediatric Society,
but also from the following entities:

- the "Center of Disease Control (*Centers for Disease Control and Prevention. Managing acute diarrhea among children : oral rehydration maintenance and nutritional therapy. MMWR 2003;52 (N°: RR16*)),

- the Italian Society of Paediatric Hepatology and Gastroenterology (*Guarino A, Albano F. Guidelines for the approach to outpatient children with acute diarrhea. Acta Paediatr 2001;90:1087-95*),

- An international working group (India, Holland, United kingdom, USA, Thailand) who issued recommendations on the management of diarrhea in the adult segment which have been extended to the paediatric field "the drug Racecadotril is described as an efficient intestinal antisecretory agent for the treatment of acute diarrhea in adults and children" (*Mantsathit S, DuPont HL, Farthing M, Kostchaiwat C, Leelakusolvong S, Ramakrishna BS, Sabra A, Speelman P, Surangsrirat S. Guideline for the management of acute diarrhea in adults. J Gastroenterology Hepatol 2002;17:S54-S71*).

9.5 Need for special diagnostic or treatment facilities and skills

No special diagnostic or treatment facilities are required for the treatment of patients in acute diarrhea.

It is extremely difficult for a doctor to assess the severity of a diarrheal episode and to what extent this episode could develop. Therefore the use of a SRO coupled with an intestinal antisecretory agent is critical in children

10. Summary of comparative effectiveness in a variety of clinical settings

10.1 Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

Among all the clinical studies performed on Racecadotril, only the controlled and most significant ones related to pediatric use have been selected.
595 children have been evaluated in clinical trials and 312 have been treated with Racecadotril.

In adults:
1,883 subjects evaluated in clinical trials
1,439 subjects treated with Racecadotril:

. At least 15 days : 840
. At least 1 month : 760
. At least 2 months : 194
. At least 3 months : 100

10.2 Summary of available estimates of comparative effectiveness (appraisal of quality, outcome, measures, summary of results)

The antidiarrheal effect of Racecadotril, paediatric form, was evaluated during four clinical studies:

- three controlled double blind studies, two compared it to a placebo in 3-month to 4- or 5-year-old hospitalised children, the other in comparison with a reference drug, loperamide in children over 2 years,
- a pharmacokinetic open dose study in a hospital setting comprising an evaluation of efficacy.

In these studies, 419 young children with acute diarrhea were included, of which 219 were treated with paediatric Racecadotril.
The distribution according to age was as follows:

- from 1 month to 2 years: 284 patients of which 150 treated with Racecadotril,
- from 2 years to 6 years: 106 patients of which 53 treated with Racecadotril,
- over 6 years: 29 patients of which 16 treated with Racecadotril.

Another study, called Cojocaru's study (164 children) is presented in the section 12.2 : *Comparative cost-effectiveness presented as range of cost per routine outcome*

For all the studies, the mean dose of Racecadotril effectively administered was 1.44 ± 0.22 mg/kg per administration (the median was 1.42 mg/kg) and the daily dosage was 3 administrations per day, just before the meal.

The making-up of oral rehydration solutions, given in each clinical study, was in compliance with the formula recommended by World Health Organisation.

The treatment was available in the form of a granulated powder containing 1% Racecadotril and 96.65% sucrose to mask the bitter taste and the characteristic odour of the active ingredient.

The maximum duration of the treatment was 7 days.

During a first stage, we will study the results of the efficacy of Racecadotril and, in a second stage, we will evaluate the tolerance results.

The clinical experience previously gained in adults contributes significantly to the demonstration of the clinical efficacy of Racecadotril in acute diarrhea. It is consequently justified to repeat these trials, conducted at the same dosage as that used in children.

Name of Company : Bioprojet Pharma Name of Finished Product : Tiorfan ® Pediatric form Name of Active substance : Racecadotril	SUMMARY OF CLINICAL TRIALS	

Table-1: Summary of paediatric placebo controlled studies -

Ref. Volume Page	- investigator - coordinating - centre(s) - Report n°	Design	Number of subjects	Diagnosis + criteria for inclusion	Duration of treatment	Test product Dosage regimen Route of administration	Criteria for evaluation	Results (efficacy)	Adverse Reactions
Table n°P-02	Pr Cezard Pr 92-13	DB vs placebo	Incl.: 172 An.: 89 R + 83 P Children aged from 3 months to 4 years	Hospitalization for acute diarrhea	Until recovery or maximum of 5 days	R 1.5 mg/kg, 3 times a day P: same posology ORS if needed	Stool yield in the first 48 hrs for the whole population and for patients with Rotavirus +	*Stool yield in first 48 hrs:* *All population (g/hr;m±SD):* *R=9.3±11.6 (n=84) vs P=15.1±14.7 (n=82) (p<0.01)* *Rotavirus positive (g/hr;m±SD):* *R=8.7±6.9 (n=24) vs P=19.6±15.3 (n=31) (p=0.001)*	AE: R=10 vs P=11. No severe AE in relationship with the studied drug
Table n°P-04	Pr.Lindo Pr 93-03	DB vs placebo	Incl.: 135 An.: 68 R + 67 P Boys aged from 3 to 60 months	Hospitalization for acute diarrhea	Until recovery or maximum of 5 days	R 1.5 mg/kg, 3 times a day P: same posology ORS if needed	First 48-hr stool output for the whole population and for patients with rotavirus +	Stool weight in the first 48 hrs (g/kg/hr): R=18.4±17.3 vs P=30.5±23.4 (p<0.005) Rotavirus positive: R(n=34) =21.3±19.4 vs P (n=39) = 35.8 ±25.1 (p<0.0005)	Symptoms of ileus spontaneously cured Mild or moderate AEs: R=8 vs P=5

Table -2: Summary of paediatric non-controlled studies -

Ref. Volume Page	Investigator Coordinating - Centre(s) - Report n°	Design	Number of subjects	Diagnosis + criteria for inclusion	Duration of treatment	Test product Dosage regimen Route of administration	Criteria for evaluation	Results (efficacy)	Adverse Reactions
Table n°P-01	Pr. Debbabi Pr Olive Pr 90-05A	Open Children aged from 6 weeks to 1 year	10 for efficacy and tolerance and 6 for the pharmacokinetics	Acute diarrhea Blood samples at T0, T1hr, T2hr, T4hr, T8hr	≤ 3 days	1.5 mg/kg at once, then 12 hrs later and after 1.5 mg/kg every 8 hrs	Pharmacokinetic parameters: AUC, Cmax, Tmax Clinical endpoints: number and characteristics of stools	Tmax: 2 hrs 30 Plasmatic concentration: stable for 4 hrs (80nmol/hr) Inhibition of enkephalinase: 50% Decrease by 80% of the number of stools after 1 day of treatment	No AE

Table -3: Summary of paediatric controlled studies with reference therapies.-

Ref. Volume Page	Investigator coordinating centre(s) Report n°	Design	Number of subjects	Diagnosis + criteria for inclusion	Duration of treatment	Test product Dosage regimen Route of administration	Reference therapy Dose regimen Route of administration	Criteria for evaluation	Results (efficacy)	Adverse Reactions
Table n°P-03	Pr. Turck Pr 93-09	DB vs Lope-ramide	Incl.: 102 An.: 52 R + 50 L. Children aged from 2 to 10 years	Acute diarrhea	Until recovery or maximum of 5 days	R 1.5 mg/kg, 3 times a day ORS if needed	Loperamide: 4 drops/kg 3 times a day + ORS if needed	• Safety: constipation • Efficacy: Number of diarrheic stools during the whole diarrheic episode	Number of diarrheic stools during the episode: R=2.7±0.4 vs L=2.1±0.4 (NS)	Patients with secondary constipation R=9 vs L=19 (p=0.03)

Controlled double blind study against placebo of Racecadotril in 3-month to 4-year-old children with acute diarrhea [Table No. P-02] - Pr. Cezard

This multicentre trial included 172 children hospitalised for severe acute diarrhea, rehydrated with an oral rehydration solution.

The main evaluation criterion was the measurement of the stool output for the first 48 hours (stool weight expressed in terms of the body weight) considered as a primary objective criterion. The secondary criteria were the stool output for the first 24 hours, the duration of diarrhea, the treatment duration and dehydration status.

Analysis of the main efficacy criterion (analysis "as intention to treat") was conducted in 149 children, of which 73 received Racecadotril and 76, the placebo. Per protocol analysis of this same criterion was conducted in 143 children (71 in the Racecadotril group, 72 in the placebo group).

The homogeneity of the groups was assessed for the characteristics of the patients, especially their age (comparison of the mean ages) and their weight (mean age: 13 months; range = 1.6 months to 3.6 years).

	Placebo	Racecadotril
0 - 3 months	-	1
3 - 6 months	13	23
6 months - 1 year	34	32
1 year - 2 years	24	21
2 years - 4 years	12	12
Mean age ± SEM [months]	13.6 ± 1.0 *(n = 83)*	12.0 ± 0.9 *(n = 89)*

The characteristics of diarrhea and its duration (2 days) at the inclusion, were comparable in the two groups. The number of stools 24 hrs before the inclusion was high, on average 6.0 ± 0.3 stools in the Racecadotril group and 6.5 ± 0.4 stools in the placebo group.

Stools culture done in 162 children showed bacteriological infection in 18% of the children treated with Racecadotril and 12.5% in the placebo group. The frequency of rotavirus infections, tested in 146/172 patients, confirmed the prevalence of this virus as a cause of winter diarrhea in young children: 67 patients with rotavirus positive, homogeneously divided between the two groups.

The mean dose of Racecadotril administered was 1.50 ± 0.03 mg/kg per administration, three times per 24 hours.

Results:

Table-4 - Efficacy of Racecadotril in Cézard's study (Intent-to-treat analysis)

Evaluation criteria	Placebo	Racecadotril	*P*
Stool weight up to 48 hours (or recovery) (g/hour) *	15.1 ± 14.7 *(n = 82)*	9.3 ± 11.6 *(n = 84)*	< 0.01
Stool weight for the first 24 hours (g/hour) *	16.3 ± 16.7 *(n = 82)*	10.8 ± 14.3 *(n = 84)*	<0.05
Frequency of dehydration† [Na^+/K^+<1] at 24 hours (%)	53.3% *(n = 60)*	24.1% *(n = 54)*	0.001

* : m ± SD Stool weight expressed as raw data (without transformation)

† : As intention to treat: patients for whom the results for urinary electrolytes were available.

There was no evidence of any significant effect of any of covariates (age, sex, bodyweight at baseline, Rotavirus status). As the data were not normally distributed, they were transformed by log and expressed as geometric means. The estimate of treatment difference was expressed as the ratio

of these geometric means with its 95% confidence interval (CI). The total stool weight on Racecadotril was nearly 50% (per protocol analysis) to 60% (intent to treat analysis) of that on placebo.

Table -5 Estimated geometric means of stool weight in Cézard's study

Evaluation criteria*	Placebo	Racecadotril	Ratio	95% CI
Stool weight up to 48 hours (or recovery) – intent to treat analysis	8.98 *(n = 82)*	5.50 *(n = 84)*	0.61	0.43 – 0.88
Stool weight for the first 24 hrs – intent to treat analysis	9.31 *(n = 82)*	6.02 *(n = 85)*	0.65	0.44 – 0.95

* : stool weight (g/hour) expressed after log transformation as geometric mean, with the ratio of the geometric means of the two groups and the 95% confidence interval (CI) of this ratio.

The efficacy of the treatment is highly significant on the primary efficacy criterion and on all the secondary criteria, whatever the Rotavirus status: stool output for the first 48 hours (or recovery), output of the stools for the first 24 hours, dehydration index (urinary Na^+/K^+ <1).

Controlled double blind study, against loperamide, of Racecadotril in boys 2-year to 10-year-old with acute diarrhea [Table No. P-03] - Pr. Turck

The objective of this multicentre trial was to compare the efficacy and clinical tolerance of Racecadotril and loperamide treatments in 102 boys aged over 2 years (as loperamide is contraindicated in children under 2 years) who suffered from acute diarrhea. 19 general practitioners took part in this trial.

The main efficacy criterion was the number of diarrheal stools assessed during the entire diarrheal episode. The duration of diarrhea, the number of associated treatments, the variation of the abdominal circumference and the frequency of rebound constipation were secondary efficacy and tolerance criteria.

The dosage recommended for each of the two treatments was administered according to their presentation. It was thus necessary to use the double placebo methodology: placebo solution for loperamide, granulated placebo powder for Racecadotril (3 times per day).

Fifty-two children received Racecadotril and 50 children received loperamide.

The homogeneity of the groups was assessed, particularly by age distribution:

Age	Racecadotril	Loperamide
2 - 4 years	27	24
4 - 6 years	9	13
6 - 12 years	16	13

The characteristics of diarrhea were comparable in the two groups: duration (less than 2 days) and identical number of stools within the last 24 hours (about 5 stools/24 hrs).

The mean unit dose of Racecadotril administered was 1.34 ± 0.02 mg/kg per administration, three times per day. The mean unit dose of loperamide administered was 4 ± 0 drops/kg.

The *results* are expressed in the table below:

Table-6 – Turck's study (acute diarrhea in children): efficacy of Racecadotril versus *loperamide*

	Racecadotril	Loperamide	*P*
- Duration of diarrhea [hours]*	10.7 ± 1.7 (n = 50)	8.8± 2.3 (n = 47)	NS
- Mean number of diarrheic stools during the diarrheal episode**	2.7 ± 0.4 (n = 51)	2.1 ± 0.4 (n = 47)	NS
- Duration of treatment [days]	1.9 ± 0.2 (n = 49)	1.8 ± 0.3 (n = 50)	NS
- Number of patients having had a change of associated treatments	10 / 52	19 / 50	0.04
- Number of constipated patients [24 hours without stools]	19 / 52	29 / 52	0.03

(m ± SEM) *: For sub-population of patients recovered and capable of being assessed (4 patients were excluded as mentioned below); **: 4 patients could not be assessed (1 in the Racecadotril group, 3 in the loperamide group) because diary cards were incomplete.

In this controlled trial, the antidiarrheal efficacy of Racecadotril is comparable to that of loperamide.

However, Racecadotril is different from loperamide on two criteria, which are important for treatment tolerance: firstly, the use of associated treatments (for pain, vomiting and constipation mainly) and, secondly, the incidence of rebound constipation, both significantly less frequent with Racecadotril than with loperamide**.** This was also observed during the two studies comparing Racecadotril and loperamide in adults. These results confirm the benefit of the absence of transit reducing effect observed in animals and healthy volunteers [Table No. 4].

Controlled double-blind study against placebo of Racecadotril in hospitalised children aged 3 - 60 months suffering from acute watery diarrhea [Table No. P-04] - Pr. Salazar Lindo

In this study,135 children were hospitalised in a single centre for severe acute watery diarrhea and rehydrated with an oral rehydration solution.

The main efficacy criterion was the measurement of the stool output for the first 48 hours (stool weight expressed in terms of body weight). The secondary criteria were total stool output (per kg of patient weight at inclusion) during either the whole diarrhea episode or during 5 days (patients not recovered within 5 days), duration of diarrhea, number of recovered patients and total ORS intake.

Analysis of the main efficacy criteria (intention to treat analysis) was conducted on 135 children, of which 68 received Racecadotril and 67 placebo. Per protocol analysis of this same criteria was conducted in 117 children (61 in the Racecadotril group, 56 in the placebo group).

All patients were male recruited in one centre by three different investigators. The mean age of the patients was just over 1 year: 13 months in the Racecadotril group and 12.5 months in the placebo group. The oldest child was 35 months old and the youngest 3 months. The children in the two groups were similar with respect to height, weight, abdominal circumference and body temperature. The majority of patients in both groups had no dehydration.

	Racecadotril	Placebo
Aged up to 24 months	64	63
Aged over 24 months	4	4
Mean age ± SD (months)	13.0 ± 6.8	12.5 ± 7.1

90% of the patients in both groups had received no prior medication for the current episode of diarrhea.. The percentage of children with stools described as loose at inclusion was 24% in the Racecadotril group and 21% in the placebo group. The mean number of stools in the previous 24 hours was 8.6 in the Racecadotril group and 9.7 in the placebo group, though the greatest number of stools passed by one patient was in the Racecadotril group: 29 stools.
Three patients (2 on Racecadotril and one on placebo) did not have their rotavirus status assessed. Of the remaining patients, 34/66 (51.5%) on Racecadotril and 39/66 (59.1%) on placebo were rotavirus positive. Four patients (two on Racecadotril and two on placebo) had no stool culture done. Of the remaining patients, 25/66 (37.9%) on Racecadotril and 28/65 (43%) had positive cultures.
The mean dose of Racecadotril administered was 1.47 ± 0.18 mg/kg per administration, three times a day.

Results:

Table -7 – Salazar-Lindo's study: Intention-to-treat analysis - All patients

Evaluation criteria	Racecadotril + ORS *(n=68)*	Placebo + ORS *(n=67)*	*P*
48 hours stool output/body weight (g/kg)	92.2 ± 97.2	169.6 ±124.5	0.0001
Stool weight per hour (48 h) (g/kg/hr)	18.4 ± 17.3	30.5 ± 23.4	<0.0005
Total stool output/body weight (g/kg)	156.5 ± 220.2	331.0 ± 320.9	0.0001

m ± SD

Table -8 - Salazar-Lindo's study: Intention-to-treat analysis - Rotavirus positive patients

Evaluation criteria	Racecadotril + ORS *(n=34)*	Placebo + ORS *(n=39)*	*P*
48 hours stool output/body weight (g/kg)	104.6 ± 96.9	194.7 ± 125.3	0.0001
Stool weight per hour (48 h) (g/kg/hr)	21.3 ±19.4	35.8 ± 25.1	<0.0005
Total stool output/body weight (g/kg)	174.4 ± 210.8	396.7 ± 353.0	0.0001

m ± SD

Table -9 - Salazar-Lindo's study: -Per Protocol analysis - All patients

Evaluation criteria	Racecadotril + ORS *(n=61)*	Placebo + ORS *(n=56)*	*P*
48 hours stool output/body weight (g/kg)	83.9 ± 91.5	173.0 ±131.8	0.0001
Stool weight per hour (48 h) (g/kg/hr)	16.7 ± 15.8	30.8 ± 24.7	<0.0005
Total stool output/body weight (g/kg)	133.0 ± 202.0	322.7 ± 340.4	0.0001

m ± SD

Table -10 - Salazar-Lindo's study: Per Protocol analysis - Rotavirus positive patients

Evaluation criteria	Racecadotril + ORS *(n=30)*	Placebo + ORS *(n=33)*	*P*
48 hours stool output/body weight (g/kg)	92.7 ± 92.9	197.0 ±131.2	0.0001
Stool weight per hour (48 h) (g/kg/hr)	18.8 ± 18.2 (n=30)	35.9 ±26.3	<0.0005
Total stool output/body weight (g/kg)	138.3 ± 179.8	385.6 ± 372.7	0.0001

m ± SD

Table -11 - Salazar-Lindo's study: Duration of diarrhea: estimated median times

Population	Rotavirus	Racecadotril	Placebo
Intention-to-treat	Negative	28 hours (n=32)	52 hours (n=27)
	Positive	28 hours (n=36)	72 hours (n=40)
Per protocol	Negative	24 hours (n=30)	44 hours (n=23)
	Positive	27 hours (n=31)	72 hours (n=33)

Table-12 - Salazar-Lindo's study: Total oral rehydration solution intake: estimated means (square rooted data, √ml/kg)

Population	Racecadotril	Placebo	Estimated difference
Intention-to-treat	9.49 (n=68)	14.61 (n=67)	-5.12 (35% reduction)
Per protocol	9.48 (n=61)	14.57 (n=56)	-5.10 (35% reduction)

The results of the study provide strong evidence that Racecadotril is an effective treatment for acute watery diarrhea in hospitalised infants and young children. The severity of the disease was demonstrated by the high mean number of stools at admission to the hospital (more than 8 diarrheal stools within the last 24 hours).

Patients treated with Racecadotril (1.5 mg/kg, tid, every 8 hours) as compared to placebo had a reduction, clinically consistent and highly significant (p=0.0001) of the 48-hour stool output, the total stool output up to recovery, the total oral rehydration solution intake and the duration of diarrhea.

The study shows that as an adjunct to oral rehydration therapy and maintenance of normal feeding recommended by WHO, Racecadotril significantly improves the course of acute diarrheal disease in infants. The antidiarrheal effect is obtained more rapidly than with ORS alone, particularly in infants with rotavirus infection.

There was a low incidence of adverse events (comparable to placebo), none of which was severe.

This study shows that Racecadotril provides a benefit in addition to ORS therapy and corresponds to the criteria requested by WHO for an effective treatment in diarrhea, i.e., decrease of stool output, reduction of duration of diarrhea, reduction in ORS requirement and good tolerance.

Open dose study of the pharmacokinetics and efficacy of Racecadotril in hospitalised children [Table No. P-01] - Pr Debbabi

This study comprised an analysis of the antidiarrheal efficacy of Racecadotril.
Ten children were hospitalised for severe watery diarrhea (7.5 liquid stools on average at the time of inclusion) present for more than 7 days.
The children were 1 year old or younger (mean age 11.4 months).

The dose administered was on average 1.45 ± 0.07 mg/kg per administration, administered 1 to 6 times.

The clinical efficacy, evaluated on the number and consistency of stools, is summarised in the table below:

Number of stools at the time of inclusion		Number of stools on D1		Number of stools on D2	
Liquid	Total	Liquid	Total	Liquid	Total
7.5 ± 0.6	7.5 ± 0.6	1.5 ± 0.5	3.1 ± 0.2	0	1.6 ± 0.2

m ± SEM

The mean number of liquid stools passed was reduced from about 7.5 to 1.5 within 24 hours, whereas at the time of inclusion, the diarrhea persisted without improvement for nearly 8 days (3 to 21 days).

Conclusion: efficacy of Racecadotril in children

In the paediatric clinical trials, Racecadotril appears to be very effective in the treatment of acute diarrhea in children (on 419 patients), thus confirming the results obtained in more than 3000 adult patients.

The duration of the treatment is 2 days on average in children and the mean daily dosage is 4.5 mg/kg administered in 3 doses, in a granulated powder form, precisely delivered.

The antidiarrheal activity of Racecadotril is significantly greater than that of placebo on all the efficacy criteria studied and in particular on the most important criterion, the stool output for the first 24 and 48 hours in children aged from 1 month to 4 years. Likewise, the activity of Racecadotril was significantly greater on the other signs associated with diarrhea, such as dehydration in infants.

In children over 2 years, age below which antimotility agents such as loperamide are contraindicated, Racecadotril is as effective as loperamide to treat the diarrhea itself and more effective than loperamide to treat associated symptoms, as the lowest frequency of abdominal pain and vomiting caused fewer associated treatments with Racecadotril.

Furthermore, the low incidence of rebound constipation with Racecadotril, significantly less frequent than that observed with loperamide, confirms the total absence of intestinal transit reduction, demonstrated experimentally in animals and in clinical pharmacology, as well as in clinical trials in adults.

Thus, the clinical experience, obtained in 4 clinical studies in children with the paediatric formulation has shown the rapid intestinal antisecretory action of Racecadotril, previously demonstrated directly in animals and healthy volunteers receiving cholera toxin.

This antisecretory effect is an indication of the reduction of stool output leading to a reduction of the major risks linked to dehydration in children, even in moderate climates.

In addition, there is maintenance of the intestinal transit time preventing stasis in the distended intestinal lumen, and consequent bacterial proliferation in the small intestine. These are the major risks associated with morphinomimetics in children, thus the lack of effect on intestinal transit time - constitutes an advantage for Racecadotril.

In children under 2 years, in whom the blood-brain barrier is immature and any treatment with morphinomimetics is contraindicated because of the risk of depression of the central nervous

system, Racecadotril constitutes a valuable symptomatic treatment for diarrhea as a supplement to the administration of an oral rehydration solution.

Different ethnic groups

In addition to the studies in children conducted in countries such as Tunisia, Peru and France, SmithKline Beecham conducted, in collaboration with Bioprojet Pharma, a large randomised, single blind trial, with 21 centres from fourteen countries (Brazil, Cameroon, Costa Rica, Guatemala, Indonesia, the Ivory Coast, Kenya, Nigeria, Mexico, Morocco, the Philippines, Pakistan, Tunisia and Vietnam). 945 **adult** outpatients suffering from acute diarrhea were included. Patients took one 100mg capsule of Racecadotril or 2mg capsule of loperamide three times a day until recovery (two consecutive normal stools instead of one or 12 hours without stool) for a maximum of 7 days. The primary efficacy criterion was the duration of diarrhea, after initiation of treatment until recovery. The secondary efficacy variables were the duration of abdominal pain and distension, the occurrence of constipation (no stools during 36hrs at least) and the overall clinical response (success/failure).

Results: Homogeneity of groups at baseline has been checked (age, weight, men/women, duration of diarrhea prior to inclusion, number of watery stools in the preceding 24 hrs). For both groups, the median duration of diarrhea at entry was 2 days and the median number of watery stools in last 24 hours was 5. The global rate of withdrawals was low (5.6%) and the distribution was well balanced between the groups.

The rapidity of diarrhea resolution was similar in the two groups of treatment: medians were 55.0 [95% Confidence interval, 48 – 66] hours with loperamide and 55.0 [50 – 65] hours with Racecadotril (intention-to-treat analysis) and 48.0 [46 – 49] hours with loperamide and 48.0 [47 – 51] hours with Racecadotril (per protocol analysis). But sometimes, concomitant medications were needed in order to relieve diarrhea: 9 other antidiarrheal agents + 6 ORS in the loperamide group *versus* 4 other antidiarrheal agents + 1 ORS in the Racecadotril group.

The changes from visit 1 to visit 2 in the occurrence of associated symptoms indicated significant difference between the two therapeutic groups for abdominal pain (P=0.024) and abdominal distension (P=0.035). The duration of abdominal distension was highly different: the median was 24.4 hours with loperamide *versus* 5.4 hours with Racecadotril (P = 0.0001). Secondary constipation was significantly more frequent with loperamide than with Racecadotril (P = 0.001) and adverse events occurred in 23.8 % and 11.5 % respectively. The overall clinical response was not different with a success rate of 93% with loperamide and 92% with Racecadotril.

11. Summary of comparative evidence on safety

11.1 Estimate of total patient exposure to date

In total 11.2 Millions children have already been treated with Racecadotril : 59% with 10mg form for infants and 41% with 30mg form for children.

In France, from November 2000 to December 2006, the total number of infants and children who were treated in France by Racecadotril was greater than 8.5 million. Safety management reports 28 adverse events (AE), that is a prevalence less than one for 304 000 patients. Among these 28 AE, 20 full case reports were available. The intrinsic imputability was known for 14 case reports: it was considered "I_4" (very likely) in 2 cases, "I_3" (likely) in 2 cases, "I_2" (plausible) in 3 cases and "I_1" (dubious) in 7 cases.
In Europe (except France), from November 2002 to December 2006, more than 1.1 million of paediatric patients were treated, and they were 12 safety case reports.

In Latin America, from January 2004 to December 2006, more than 500 000 paediatric patients were treated without reported ADR.

11.2 Description of adverse effects/reactions

During clinical trials (see 10.2 for details):

The most commonly reported undesirable effects are vomiting, fever and respiratory disorders, occurring in more than 1% of patients. No alterations of the central nervous system have been observed.

Table of main adverse events according to System Organ Classification (MedDRA)

System Organ	Frequency	Adverse events
Respiratory disorders	Common	
Gastrointestinal disorders	Common	Vomiting
Skin and subcutaneous and tissue disorders	Uncommon	Contact dermatitis -Cutaneous eruption – Erythema – Rash.
General disorders	Common	Fever

Commun (> 1/100, < 1/10), Uncommon (> 1/1 000, < 1/100).

Post Marketing pharmacovigilance

The overall most frequent Adverse Events were cutaneous and/or allergic: mainly rash, erythemous/papulous reaction, prurigo or urticaria, but also few cases of multiform erythema, erythema nodosum, lip or tongue oedema, angioneurotic oedema and Quincke oedema.

Drug-drug interactions.

No drug interaction has been reported.

11.4 Summary of comparative safety against comparators

The clinical studies listed here above demonstrate a clear superiority above other comparator drugs :

- either in terms of safety : less side effects induced by Racecadotril with the same efficacy as loperamide,

- either in terms of efficacy comparing to other classes of antidiaarheal drugs which have no scientific database to prove any action to reduce the stool output (e.g. absorbents, probiotics, activated coal, etc..).

12. Summary of available data on comparative costs and cost-effectiveness

12.1 Range of cost of the proposed medicine

The most common presentation of Tiorfan® or Hidrasec® varies from 16 to 18 sachets for both forms, which is approximately a full treatment in acute diarrhea.
In Europe some presentations are 20 and 30 sachets as well
In Latin America the pack size is 18 sachets.

The ex factory prices ranges from 5 to 8 euros depending upon the pack size of course and the local market conditions and reimbursement lists.

The public price in most countries ranges from 10 to 11 euros with some exceptions in countries where market conditions, margin structures or government policies imply high variations such as in Germany.

12.2 Comparative cost-effectiveness presented as range of cost per routine outcome

The cost-effectiveness of Racecadotril treatment has been evaluated in one particular **independent** study in France in 2003 (*Cojocaru B, Bocquet N, Timsit S, Wille C, Boursiquot C, Marcombes F, Garel D, Sannier N, Chéron G. Effet du racécadotril sur le recours aux soins dans le traitement des diarrhées aiguës du nourrisson et de l'enfant. Arch Pediatr (Paris) 2002 ; 8:774-9)*

Pr. Martinot and his team have just issued an article on the therapeutic management of infants'gastroenteritis: in the section "how to assess the therapeutic strategies 'usefulness?", following observation is made : "*it is important to assess to what extent this reduction in stool output thanks to the use of Racecadotril practically helps in reducing the need for intraveneous rehydrations, the hospitalization rates or their respective durations, the secondary medical consultations*" (*Martinot A, Aurel M, Pruvost J, Hue V, Dubos F. Can the clinical epidemiology in emergency departments improve the therapeutic management in the infants' gostroenteritis cases? Arch Pediatr 2006;13: 553-*.

In the Cojocaru study, Racecadotril and rehydration was compared with rehydration alone
. Children aged 3 months to 3 years who had acute diarrhea
. Evaluated in an emergency department (Hôpital Necker Enfants Malades, Paris, France).
Primary end point :
. Number of medical visits during the week after starting treatment.
Secondary end points :
. Number of stools during the first 48 hours
. Duration of the diarrhea and the weight on day 7

	Racecadotril + rehydration *(n = 81)*	rehydration alone *(n = 83)*	*P*
Total	14 / 76 (18.4%)	27 / 78 (34.6%)	< 0.05
Initial hydration			
- PO	10 / 41	15 / 41	NS
- IV	4 / 35	12 / 37	< 0.05
Reason for consultation			
- Same episode of diarrhea	8 / 76	21 / 78	< 0.05
Concern *Worsening* *Secondary hospitalisation*	*6* *2* *2*	*8* *13* *8*	
- Other reason	6	6	
Days of hospitalisation for infusion (number of children)	37 (37)	45 (43)	

The need for a second visit at the hospital and the need for IV rehydration have been cut by half thanks to Racecadotril in addition to ORS.

Therefore the cost effectiveness calculated in economic evaluations, the benefits of Racecadotril treatment in acute diarrhea is extremely high :

- considering the high cost of hospitalization(from USD 60 –in 2001- in Peru to 2,672 in the US). Overall the costs for hospitalization were USD 2.6 Millions in Peru and USD 274 Millions in the US.
- reduces mortality rate thanks to a better observance of ORS

13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

COUNTRIES	BRAND NAME	DATES of MARKETING AUTHORISATIONS	DATES of LAUNCHES
STATUS OF REGISTRATIONS IN the EUROPEAN UNION			
Bulgaria	HIDRASEC	Apr-05	juin-05
France	TIORFAN	Sep-99	nov-00
Germany	TIORFAN	Jun-04	août-04
Greece	HIDRASEC	Apr-04	mai-06
Italy	TIORFIX	Pending	N/A
Portugal	TIORFAN	Aug-04	mai-05
Romania	HIDRASEC	Aug-04	juin-05
Spain	TIORFAN	Jun-02	Nov-02
STATUS OF REGISTRATIONS outside the EUROPEAN UNION			
Marocco	TIORFAN	Pending	N/A
Tunisia	TIORFAN	mars-04	mai-04
Indonesia	HIDRASEC	Pending	N/A
Philippines	HIDRASEC	Nov-05	avr-07
Thaïland	HIDRASEC	Aug-05	N/A
Vietnam	HIDRASEC	Oct-05	avr-07
Agentina	HIDRASEC	Pending	N/A
Brasil	TIORFAN	Apr-04	sept-06
Chile	HIDRASEC	Dec-04	oct-06
Costa Rica	HIDRASEC	Sep-04	août-05
Dominican Republic	HIDRASEC	Sep-04	avr-05
Ecuador	HIDRASEC	Aug-04	mai-05
El Salvador	HIDRASEC	Jan-05	mai-05
Guatemala	HIDRASEC	Aug-04	août-04
Honduras	HIDRASEC	Jul-04	mai-05
Mexico	HIDRASEC	Oct-03	déc-03
Nicaragua	HIDRASEC	Jul-04	avr-05
Panama	HIDRASEC	Mar-04	août-06
Paraguay	HIDRASEC	Apr-05	sept-05
Peru	HIDRASEC	Dec-03	mars-04
Venezuela	HIDRASEC	Sep-05	avr-06

14. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopeia)

British Pharmacopoeia: No
International Pharmacopoeia: No
United States Pharmacopoeia: No

A European Pharmacopoeia Monograph of Racecadotril is currently under progress.

15. Proposed (new/adapted) text for the WHO Model Formulary (using Tiorfan as the example of the listed drug)

Description

TIORFAN 10mg / 30mg is an intestinal antisecretory agent used for the treatment of diarrhea.

TIORFAN 30mg is used for the treatment of symptoms of acute diarrhea in children over three months of age. It should be used together with an abundant liquid intake and the usual dietary measures, when these measures are not sufficiently effective on their own to control the diarrhea.

Before you use TIORFAN

Do not use TIORFAN

- If your child is allergic (*hypersensitive*) to Racecadotril or any of the other ingredients of TIORFAN .
- If you have been told by your doctor that your child has an intolerance to some sugars, ask your doctor before you give TIORFAN to your child.

Take special care with TIORFAN

You should tell your doctor if:
- your child is under three months of age,
- there is blood or pus in your child’s stools and he/she has fever. The cause of his/her diarrhea may be a bacterial infection that should be treated by your doctor,
- your child is suffering from chronic diarrhea or diarrhea caused by antibiotics,
- your child is suffering from prolonged or uncontrolled vomiting,
- your child is suffering from kidney disease or impaired liver function,
- your child is suffering from diabetes (see “Important information about some of the ingredients of TIORFAN”).

Taking other medicines

Please tell your doctor if your child is taking or has recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding

Use of TIORFAN is not recommended in case of pregnancy and breast-feeding.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

TIORFAN 30mg has little or no effect on the ability to drive and use machinery.

Important information about some of the ingredients of TIORFAN

TIORFAN 30mg contains about 3g of sucrose (saccharose) per sachet.
If you have been told by your doctor that your child has an intolerance to some sugars, ask your doctor before you give TIORFAN to your child.

In children with diabetes, the quantity of sucrose ingested with TIORFAN 30mg should be taken into account in the child's total daily intake of sugar.

3. HOW TO USE TIORFAN 30mg (TIORAFN 30mg is used as an example)

Dosage and instructions for use
TIORFAN 30mg is supplied in the form of granules to be swallowed.
It can be added to food or mixed with water in a glass or baby bottle. Mix well and give immediately to your child.

The recommended daily dose depends on your child's weight: 1.5mg/kg per dose (corresponding to 1 to 2 sachets), three times daily at regular intervals.

In children from 30 months to 9 years of age (weighing about 13-27 kg): one sachet per dose.
In children of more than 9 years of age (approximate weight of more than 27 kg): two sachets per dose.

Always give TIORFAN 30mg to your child exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Duration of treatment
Your doctor will tell you how long the treatment with TIORFAN 30mg will last. It should be continued until your child has two normal stools, not exceeding 7 days.

Dietary advice
To compensate for the loss of liquid due to your child's diarrhea, make sure that he/she drinks a lot throughout the day.

If you give more TIORFAN than you should
If your child has taken more TIORFAN than he/she should have, contact your doctor or pharmacist immediately.

If you forget to give TIORFAN

Do not give a double dose to your child to make up for a forgotten dose. Simply continue with the treatment.

Possible side effects

Like all medicines, TIORFAN can cause side effects, although not everybody gets them.
The most common side effects in children are vomiting and fever (at least 1 in 100 patients). These side effects also occur in acute diarrhea.
The following uncommon side-effects have been reported (at least 1 in 1,000 patients):
- reduced level of potassium in the blood (hypokalemia),
- intestinal obstruction (ileus),
- spasmodic contraction of the bronchi (bronchospasm).
In rare cases (at least 1 in 10,000 patients), skin rashes have been reported.
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.

How to store Tiorfan

Keep out of the reach and sight of children.
Do not use TIORFAN after the expiry date which is stated on the sachet and on the outer packaging after EXP. The expiry date refers to the last day of that month.
There are no special storage conditions.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

Further information

What TIORFAN 10mg / 30mg contains

The active substance is Racecadotril. Each sachet contains 10mg / 30mg of Racecadotril.
The other ingredients are sucrose, colloidal anhydrous silica, polyacrylate dispersion 30 per cent and apricot flavour.

What TIORFAN looks like and contents of the pack

TIORFAN 30mg is supplied in the form of granules for oral suspension contained in sachets.
Each pack contains 10, 16, 18, 20, 30, 50 or 100 sachets.
Not all pack sizes may be marketed.

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