HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

20 February 2008

TIORFANOR 175 mg tablets
PVC PVDC aluminium blisters
Pack of 12 (CIP: 382 003.4)

BIOPROJET PHARMA

Racecadotril
List II

Date of marketing authorisation: 26 October 2007 (national procedure)

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for hospital use.

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Racecadotril

1.2. Indication

Symptomatic treatment of adult acute diarrhoea.

1.3. Dosage

For oral use
One tablet initially at any time, then 1 tablet in the morning and 1 in the evening, i.e. 2 tablets per day.
Treatment should not continue for more than 7 days.

Specific populations:
Elderly patients: No dose adjustment appears to be necessary for elderly patients.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2007)

A : Alimentary tract and metabolism
A07 : Antidiarrhoeals
A07X : Other antidiarrhoeals (Antisecretory agents)
A07XA : Other antidiarrhoeals
A07XA04 : Racecadotril

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

Racecadotril is marketed for the same indication, symptomatic treatment of adult diarrhoea, in the form of 100 mg capsules to be taken 3 times a day (TIORFAN 100 mg capsules).

2.2.2. Medicines with a similar therapeutic aim

Symptomatic treatment of adult acute diarrhoea:

IMODIUM (loperamide – slows intestinal transit without atropine) and its generics
SMECTA (Clays – Diosmectite)

3 ANALYSIS OF AVAILABLE DATA

The efficacy of TIORFANOR (racecadotril) 175mg BID in the symptomatic treatment of adult acute diarrhoea was evaluated in two studies versus TIORFAN (racecadotril) 100mg TID, one meta-analysis and one meta-regression.

- Study P04-02: Double-blind, randomised, phase III study controlled against TIORFAN (100mg TID). Non-inferiority hypothesis.

- Study P05-12: Double-blind, randomised, phase III study controlled against TIORFAN (100mg TID). Superiority hypothesis.

- Meta-analysis (unpublished) based on individual data from the 2 phase III studies P04-02 and P05-12.

- Meta-regression (unpublished) performed on studies mainly from the Cochrane (CENTRAL), MEDLINE and EMBASE databases. The comparators were racecadotril 175mg BID, racecadotril 100mg TID or loperamide.

3.1. Efficacy

3.1.1 Study P04-02

Objectives: to compare the efficacy and safety of racecadotril 1 x 175mg tablet BID versus 1 x 100mg capsule TID in the symptomatic treatment of acute diarrhoea presumably of infective origin in 221 patients.

Methodology: Double-blind, randomised study controlled against racecadotril 100mg TID. Non-inferiority hypothesis (inferiority was found if the least favourable estimate of the difference between the products did not exceed 1 stool in favour of the reference product).

Inclusion criteria: The study was conducted on outpatients:

- male or female
- at least 18 years of age
- presenting with acute diarrhoea, presumably of infective origin, defined by the sudden onset of increased stool frequency characterised by the following 3 mandatory criteria:
    - at least 3 soft or watery stools in the last 24 hours
    - onset of diarrhoea (first diarrhoeal stool) at least 24 hours previously
    - onset of diarrhoea (first diarrhoeal stool) not more than 3 days previously.

Exclusion criteria:

- presence of blood and/or sanies in the stools
- need for antibiotic treatment
- progressive chronic gastrointestinal disease, chronic diarrhoea
- introduction of potential diarrhoea-inducing treatment within the 8 days prior to inclusion
- antidiarrhoeal treatment received for more than 24 hours during the 3 days prior to inclusion
- immunodepression, known HIV positive status
- known severe liver or kidney disease
- progressive malignant disease or non-stabilised progressive disease
- intoxication of any kind, including alcoholism
- known allergy to racecadotril
- concomitant disease likely to jeopardise compliance with the protocol.

Treatments: Patients were split into 2 groups.
The test treatment was racecadotril 175mg BID (tablets, group C175 comprising 110 patients).
The reference treatment was racecadotril 100mg TID (TIORFAN capsules, group G100 comprising 111 patients).

Treatment was given until the patients were cured[1], without exceeding 7 days.

Primary endpoint: number of diarrhoeal stools (soft or watery), based on the patient's self-completed diary card:

- for cured patients, it was the number of diarrhoeal stools passed between commencement of treatment and cure
- for non-cured patients, it was the total number of diarrhoeal stools passed throughout the duration of treatment.
- for patients leaving the study prematurely due to worsening of their diarrhoea (number of stools > baseline number after 48 hours of treatment) or due to an intercurrent event requiring discontinuation of the patient's participation in the study as determined by the investigator or the patient, the last known daily value (number of stools in the last 24 hours prior to premature withdrawal from the study) was carried over until day 7.

Secondary endpoint: the duration of diarrhoea under treatment was among the secondary endpoints studied.

Results:

Population: the number of patients included and analysed by intention to treat was 221: 121 women and 100 men with a mean age of 41.
Intention-to-treat (ITT) population: 111 cases (group G100)
110 cases (group C175)
Per protocol (PP) population: 106 cases were analysed in each of the two groups.
Patient characteristics were comparable in the two groups.

Efficacy versus active comparator:

The percentage cured at day 7 was 100% with TIORFANOR (C175) and 96.4% with TIORFAN (G100).

[1] A cure was defined as the occurrence of a 12-hour period without a stool after initiation of treatment or the passing of 2 consecutive normal stools.

Table 1: Primary endpoint results for patients on racecadotril 175mg tablets (C175) or racecadotril 100mg capsules (G100)

Population	Treatment group	N	Mean ± SD	LSM[1] ± SEM	95% CI	p[2]
ITT	C175	110	4.0 ± 3.8	1.89 ± 0.10		
	G100	111	6.2 ± 11.2	2.19 ± 0.10		
	Difference (C-G)			-0.31 ± 0.15	[-0.59; -0.02]	<0.0001
PP	C175	106	3.7 ± 3.1	1.85 ± 0.08		
	G100	106	4.6 ± 4.1	2.05 ± 0.08		
	Difference (C-G)			-0.18 ± 0.12	[-0.41; 0.05]	<0.0001

[1] Least squares means: data were square-root transformed and adjusted according to baseline severity.
[2] For a non-inferiority limit of 0.40 for square-root transformed data.

TIORFANOR (C175) was non-inferior to racecadotril 100 mg TID on number of diarrhoeal stools by both intention to treat and per protocol (non-inferiority hypothesis: 95% CI, threshold δ=-1 stool).

The actuarial duration of diarrhoea (secondary endpoint) was 13.7 h in group C175 versus 17.5 h in group G100.

3.1.2 Study P05-12

Objectives: to compare the efficacy and safety of racecadotril 1 x 175mg tablet BID versus 1 x 100mg capsule TID in the symptomatic treatment of acute diarrhoea presumably of infective origin.

Methodology: Double-blind, randomised study controlled against racecadotril 100mg TID. Superiority hypothesis.

Inclusion criteria: The study was conducted on outpatients:

- male or female
- at least 18 years of age
- presenting with acute diarrhoea, presumably of infective origin, defined by the sudden onset of increased stool frequency characterised by the following 3 mandatory criteria:
    - at least 3 soft or watery stools in the last 24 hours
    - onset of diarrhoea (first diarrhoeal stool) at least 24 hours previously
    - onset of diarrhoea (first diarrhoeal stool) not more than 3 days previously.

Exclusion criteria:

- presence of blood and/or sanies in the stools
- need for antibiotic treatment
- progressive chronic gastrointestinal disease, chronic diarrhoea
- introduction of potential diarrhoea-inducing treatment within the 8 days prior to inclusion
- antidiarrhoeal treatment received for more than 24 hours during the 3 days prior to inclusion
- immunodepression, known HIV positive status
- known severe liver or kidney disease
- progressive malignant disease or non-stabilised progressive disease
- intoxication of any kind, including alcoholism
- known allergy to racecadotril
- concomitant disease likely to jeopardise compliance with the protocol.

Treatments: Patients were split into 2 groups.
The test treatment was racecadotril 175mg BID (tablets, group C175 comprising 117 patients).
The reference treatment was racecadotril 100mg TID (TIORFAN capsules, group G100 comprising 118 patients).

Treatment was given until the patients were cured, without exceeding 7 days.

Primary endpoint: number of diarrhoeal stools (soft or watery), based on the patient's self-completed diary card, each stool was weighted for its consistency by the Powell-Tuck calculation method: normal (formed)=0; soft=1; liquid=2

- for cured patients, it was the number of diarrhoeal stools passed between commencement of treatment and cure[2]
- for non-cured patients, it was the total number of diarrhoeal stools passed throughout the duration of treatment.
- for patients leaving the study prematurely due to worsening of their diarrhoea (number of stools > baseline number after 48 hours of treatment) or due to an intercurrent event requiring discontinuation of the patient's participation in the study as determined by the investigator or the patient, the last known daily value (number of stools in the last 24 hours prior to premature withdrawal from the study) was carried over until day 7.

Secondary endpoint: the duration of diarrhoea under treatment was among the secondary endpoints studied.

Results:

Population: the number of patients included was 235: 129 women and 106 men with a mean age of 42.
Intention-to-treat (ITT) population: 118 cases (group G100)
117 cases (group C175)
Per protocol (PP) population: 114 cases were analysed in each of the two groups.
Patient characteristics were comparable in the two groups.

Efficacy versus active comparator:

The percentage cured at day 7 was 100% by PP and 97% by ITT in each of the two groups.

[2] A cure was defined as the occurrence of a 12-hour period without a stool after initiation of treatment or the passing of 2 consecutive normal stools.

Table 2: Primary endpoint results for patients on racecadotril 175mg tablets (C175) or racecadotril 100mg capsules (G100)

Population	Treatment group	N	Mean[1] [min-max]	LSM (95% CI)[2]	p
ITT	C175	117	9.5 [0 - 70]		
	G100	118	14.4 [0 - 98]		
	Difference (C-G)[3]			-4.8 [-8.58; -1.02]	0.003
PP	C175	114	8.1 [0 - 62]		
	G100	114	11.9 [0 - 62]		
	Difference (C-G)[3]			-3.62 [-6.03; -1.22]	0.003

[1] Total number of diarrhoeal stools until cure (mean [min-max] according to the Powell-Tuck index)
[2] Least squares means: data were square-root transformed and adjusted according to baseline severity.
[3] Difference (C-G): Difference in total number of diarrhoeal stools until cure.

The reduction in the total number of non-formed (soft or liquid) stools until cure (primary endpoint) was statistically greater in group C175 than in group G100 (ITT population: C-G= -4.8 [-8.58; -1.02]).

Duration of diarrhoea (secondary endpoint) under treatment was 32.9 h ± 35.6 for group C175 and 45.3 h ± 37.9 for group G100 (ITT population Hazard ratio: 1.378 [1.06; 1.791]; p = 0.0125)

3.1.3 Other data

3.1.3.a Meta-analysis

Methodology: an unpublished meta-analysis, supplied by the company, was performed on the individual data from 2 clinical studies using a random-effects model.

Primary endpoint: total number of diarrhoeal stools until cure.
Secondary endpoint: time to cure or the interval between commencement of treatment and the time of the last diarrhoeal stool.

Results:

Studies: the number of patients included was 456 (2 phase III studies). Intention-to-treat (ITT) population: 229 patients (racecadotril 175mg BID)
227 patients (racecadotril 100mg TID)

Efficacy versus active comparator: the treatment effect was significant with a reduction in the total number of diarrhoeal stools to cure (NDS) of -2 [-3.21, -0.78] (p<0.01). The same results were obtained for both the intention-to-treat (ITT) and the per-protocol (PP) analyses.

Table 3: Meta-analysis on the primary endpoint, the total number of diarrhoeal stools until cure (NDS)

	ITT				PP			
	Coeff.	95% CI		P	Coeff.	95% CI		P
Baseline NDS	0.56	0.33	0.80	0.001	0.28	0.12	0.44	<0.001
Treatment NDS	-2.00	-3.21	-0.78	<0.001	-1.57	-2.42	-0.73	0.001

For the secondary endpoints examined for exploratory purposes, the results showed a mean duration of diarrhoea of 35.5 hours in group G100 and 25.4 hours (SD: ±29.4) in group C175. The hazard ratio observed was 0.73 [0.60; 0.87] (p=0.001), confirming the ITT treatment effect.

Table 1: Meta-analysis on the duration of diarrhoea

	ITT				PP			
	HR[1]	95% CI		P	HR[1]	95% CI		P
Duration of diarrhoea	0.73	0.60	0.87	0.001	0.76	0.62	0.91	0.008

[1] Hazard Ratio

3.1.3.b Meta regression

Objectives: to compare the efficacy of racecadotril 175mg BID with that of other treatments in adult acute diarrhoea.

Methodology: unpublished meta-regression including all the randomised controlled studies, published or not, irrespective of language. The databases searched were primarily Cochrane (CENTRAL), MEDLINE and EMBASE.

Treatment: racecadotril 175mg BID or racecadotril 100mg TID or loperamide versus placebo.

Primary endpoint: effect size in the studies, estimated by calculation of the standardised mean difference.

Results

Studies: estimated effect size (ES), defined as the primary endpoint, lacked clinical relevance according to the authors. The results were therefore interpreted according to the primary endpoints used in acute diarrhoea, i.e. duration and number of diarrhoeal stools until cure, versus placebo. A total of 12 studies (2,380 patients) were included in the meta-analysis, 7 of which met the “duration of diarrhoea” criterion and 9 the “number of diarrhoeal stools” criterion.

Efficacy compared with placebo

The results showed a reduction in the mean duration of acute diarrhoea of 17.9% [95% CI: -24.9, -10.8] in the group treated with RACECADOTRIL 100mg TID or LOPERAMIDE and 33.1% [-46.1, -18] in the group treated with TIORFANOR 175 mg BID compared with placebo.

The mean number of diarrhoeal stools was reduced by 19.3% [95% CI: -27.0, -11.7] in the group treated with RACECADOTRIL 100mg TID or LOPERAMIDE and 35.2% [95% CI: -50.5, -19.8] in the group treated with TIORFANOR 175 mg BID compared with placebo.

Table 2: Efficacy of treatments compared with placebo in acute diarrhoea

	racecadotril 100ml TID or loperamide	TIORFANOR 175mg BID
Mean relative reduction in duration (%) [95% CI]	-17.9 [-24.9, -10.8]	-33.1 [-46.1, -18.0]
Mean relative reduction in number of diarrhoeal stools (%) [95% CI]	-19.3 [-27.0, -11.7]	-35.2 [-50.5, .19.8]

3.2. Safety

Safety data for TIORFANOR 175mg BID come from two pharmacokinetics studies and two clinical studies. During the clinical studies for TIORFANOR 175mg, conducted on 456 adults, the most commonly reported adverse effects were constipation and headache, at a frequency of between 1 and 2%. These adverse effects are mentioned in the SPC as frequent adverse effects.

On the basis of study P04-02, a public evaluation report by AFSSAPS (November 2007) concluded that the treatment regimen based on racecadotril (175mg BID) was associated with a slightly increased risk of the occurrence of adverse effects compared with a treatment regimen based on racecadotril (100mg TID). Overall, these adverse effects were not serious and demonstrated the good overall safety profile of racecadotril. This study, however, highlighted cases of headache with the 175mg dose, which had not been reported with racecadotril 100mg.

3.3. Conclusion

The two clinical trials reported were randomised, double-blind with double placebo and multicentric, comparing racecadotril 175mg BID with an active comparator (racecadotril 100mg TID). The patients included in the study population were aged over 18 and had acute diarrhoea presumably of infective origin.
For the primary endpoint, “number of non-formed stools before cure”, and the secondary endpoint, “duration of diarrhoea”, one study showed non-inferiority and the other superiority of racecadotril 175mg tablets BID compared with racecadotril 100mg capsules TID. The meta-analysis supplied by the company and performed on the individual data from these two studies showed a mean relative reduction in the duration of acute diarrhoea and the number of diarrhoeal stools for the group treated with racecadotril 175mg BID.

According to the SPC, the most commonly observed adverse effects (1-2%) with the proprietary product TIORFANOR (175mg BID) were constipation and headache.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

In the vast majority of cases, acute diarrhoea is treated in an outpatients setting. Acute diarrhoea lasts for a few days and is most often caused by viruses, more rarely by bacteria (the microorganisms themselves or their toxins), and exceptionally by parasites in France. The primary danger in cases of diarrhoea is dehydration associated with electrolyte loss.
In mild cases, which are the most common, diarrhoea causes a temporary deterioration in quality of life.

This proprietary product is used as a form of symptomatic treatment.

The efficacy/safety ratio is moderate.

Insofar as the first-line treatment for acute diarrhoea is rehydration, TIORFANOR may be used as adjunctive treatment in the therapeutic strategy for this disease.

There are alternative treatments.

Adult acute diarrhoea is common but results in a low public health burden because it is not generally serious.
Improved therapeutic management of adult acute diarrhoea is not a public health need.

In view of the available data, this new dosage form of racecadotril is not expected to have an impact in terms of morbidity and quality of life for these patients.
In light of these factors, TIORFANOR is not expected to benefit public health.

The actual benefit of this medicinal product is moderate.

4.2. Improvement in actual benefit

The Transparency Committee cannot consider an increased dosage of an already existing product to be a therapeutic advance. Consequently, TIORFANOR 175mg tablets does not provide an improvement in actual benefit (IAB level V) compared with other medicinal products used in the symptomatic treatment of adult acute diarrhoea, particularly TIORFAN.

4.3. Therapeutic use

The aim of treatment for acute diarrhoea is to prevent dehydration, particularly in individuals at risk.
Oral rehydration with solutions containing electrolytes and glucose forms the basis of diarrhoea management. Intravenous injections are used in cases of severe dehydration.

As a supplement to rehydration, anti-infective treatment is recommended in certain infective forms of diarrhoea of bacterial origin. The antibiotics used depend on the microorganism identified.

Traveller's (or holiday) diarrhoea
Prevention of traveller's diarrhoea is based on observance of general hygiene measures. To correct or avoid dehydration, it is important to drink plenty of fluids and, if the diarrhoea is profuse, to use oral rehydration solutions. Mild adult forms may be attenuated and shortened by taking an anti-diarrhoeal with anti-motor or anti-secretory action. For more complete information, see the guidelines in the *Bulletin épidémiologique hebdomadaire* (BEH No 24-25/2005[3]).

4.4. Target population

The target population for TIORFANOR comprises all patients in the indication "symptomatic treatment of adult acute diarrhoea". According to the Sentinelles network (2006), the annual incidence rate is estimated at 8,650 cases per 100,000 inhabitants, or an estimated annual incidence of 5,270,000 persons [95% CI: 5,160,000; 5,380,000]. The age cohort of patients aged over 15 years comprises 3,390,000 persons[4].

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the indication and at the dosage given in the marketing authorisation.

4.5.1. Packaging: Appropriate to prescription requirements.

4.5.2. Reimbursement rate: 35%

[3] InVS, Santé des voyageurs et recommandations sanitaires 2005, BEH n°24-25/2005, p.117-127
[4] Out of a total of 5,049,248 patients, or 85.3% of total cases.