COMMENTS FROM BIOPROJET PHARMA ON THE REPORT IN RELATION TO THE Racecadotril APPLICATION FOR THE WHO COMMITTEE REVIEWING THE ESSENTIAL MEDECINES LIST FOR CHILDREN

September 2007

1.
Conclusion from the Committee:

Clinical trials were conducted only at the hospital and not with outpatients.
Lack of data in less severely affected infants.

Bioprojet Comments:

The WHO mandatory clinical endpoint in randomized clinical trials to assess efficacy of an antidiarrhoeal medicine is the stool output (in grams/day and grams/Kg bodyweight) . Therefore, in order to fully comply with this criterion, serious clinical trials can only take place in hospitals equipped with adequate beds to accurately measure the stool weight.
The hospitalized infants in the clinical trials were not all suffering severe diarrhoea: some of them were kept at the hospital to make sure that the rehydration was correctly performed by healthcare Professionals and to make sure that diarrhoea would not become more severe.
An additional statistical study is currently checking the similar efficacy for both severe end not severe cases.

2.
Conclusion from the Committee:

Limited experience in clinical trials due to the small number of patients: 307 infants to determine clinical effectiveness and safety and to assess the feasibility and acceptability of treatment regimens

Bioprojet Comments:
To date, the racecadotril clinical experience with infants & children is the largest ever clinical programme managed in acute diarrhea, and following the WHO mandatory requirements (2 RCTs, DB vs rehydration, endpoint on stool output measurement).

2.1 Effectiveness and safety: In the Periodic Safety Updated Report (PSUR) sent twice a year to the Regulatory Authorities, it is mentioned at March 31, 2007, that 685 infants and children were treated with Racecadotril in clinical studies to assess effectiveness and safety: the number of subjects with adverse events was 103 out of 685 with Racecadotril (15%), vs. 95 out of 411 (23%) with placebo and 11 out of 50 with Loperamid (22%).

2.2 Safety data: in the same PSUR, post marketing safety data report 35 adverse events for 11.2 millions patients treated with Racecadotril worldwide, i.e. with a cumulative frequency since launching of 0.0003%

2.3 Feasibility and acceptability of treatment regimens: Current regimen is 1.5 mg / kg and the intake is relatively simple at one or two sachets: it avoids any misunderstanding when following this regimen.
In addition sachets in particular for the excipient sucrose are the safest and most reliable packaging especially for emerging countries (hermetic primary packaging).

Furthermore the confusion with ORS sachets is very little since the ORS is given either in pre-mixed bottles or in sachets to be diluted with 200 ml pure water and then, the baby bottle should be stored in the refrigerator (taste masking effect and bacterial growth limitation). By contrast, the racecadotril regimen is very different: it needs only to be diluted in a small quantity of water (less than half a glass) and can be given then in one or two tea spoons.