Report on two Phase IV studies undertaken to evaluate the safety of the new Oral Rehydration Salts (ORS) solution recommended by WHO and UNICEF and that has been included in the WHO Model List of Essential Medicines in 2003.

15 May 2007

In the section on Oral Rehydration Salts (ORS) of the report of the WHO Expert Committee, 2003 (including the 13 Model List of Essential Medicines), the committee concluded that :

"… the evidence supporting the superiority of the new reduced osmolarity ORS solution for the treatment of acute non-cholera diarrhoea in children was convincing, with a 5% absolute risk reduction (NNT = 20) in the need for unplanned intravenous infusions, and on this basis recommended that the formula for ORS in the Model List (section 17.7.1 Oral hydration) be changed to 75 mEq/l sodium (sodium chloride 2.6g/l) and 75 mmol/l (13.5 g/l) glucose."

However, because the application also mentioned the fact that the reduced-osmolarity ORS solution containing 75 mEq/l sodium, 75 mmol/l glucose (total osmolarity = 245 mOsm/l) **is associated with an increased incidence of transient, asymptomatic hyponatraemia,** the committee recommended that careful monitoring be advised for significant hyponatraemia, especially in adults with cholera and treated with the new ORS solution. In addition, it also recommended the addition, in the WHO Model List of Essential Medicines, of the following footnote:

"In cases of cholera a higher concentration of sodium may be required".

Following on this comment, the Department of Child and Adolescent Health and Development decided to support Phase IV studies (Pharmacovigilance studies) to measure the rates of **symptomatic hyponatraemia** during treatment of patients with diarrhoea with the new ORS solution.

One study was conducted in Dhaka and Matlab (Bangladesh) (1) and the other in Kolkata (India).

In both sites, all patients admitted with uncomplicated watery diarrhea were treated with the newly recommended ORS and monitored. Patients developing neurological symptoms (seizure or altered consciousness) were transferred to the special care ward for treatment and investigated to identify the cause of the symptoms. Patient records of the Dhaka hospital were reviewed during the previous year when the old ORS formulation was used.

The study conducted at the Dhaka hospital (December 1, 2002-November 30, 2003) and Matlab hospital (February 2, 2003-January 31, 2004) of the International Centre for Diarrhoeal Disease Research Bangladesh, recruited 53,280 patients, including 22,536 children younger than 60 months.

The study conducted at the Infectious Diseases Hospital in Kolkata (India) (March 7, 2005 - June 30, 2006) recruited 27,966 patients, including 7,893 children less than 7 years of age.

In Bangladesh, twenty-four patients (24), none older than 36 months, developed seizures or altered consciousness associated with hyponatraemia, with an overall incidence rate of 0.05% (95% confidence interval [CI],0.03%-0.07%) at the Dhaka hospital and 0.03% (95% CI, 0.01%-0.09%) at the Matlab hospital.

During the previous year, when the old ORS formulation was used, 47 patients at the Dhaka hospital had symptoms associated with hyponatraemia, for an estimated incidence rate of 0.10% (95% CI, 0.07%-0.13%). Therefore, it appears that introduction of the new ORS formulation was associated with a significant reduction in the rates of hyponatraemia (odds ratio, 0.50; 95% CI, 0.29-0.85; *P*=.009).

In India, only two patients (10 years old and 1.5 year old) developed seizures or altered consciousness associated with hyponatraemia, for an estimated incidence rate of less than 0.007%.

Conclusion. The risk of symptoms associated with hyponatraemia in patients (adults with cholera as well as young children) treated with the reduced osmolarity ORS is minimal and did not increase with the change in formulation. For this reason we do not feel that the footnote suggesting that in case of cholera ORS solution with higher sodium content may be required is justified anymore.

1. Alam NH, Yunus M, Faruque ASG, Gyr N, Sattar S, Parvin S, Ahmed JU, Salam MA, Sack DA. Symptomatic Hyponatremia During Treatment of Dehydrating Diarrheal Disease With Reduced Osmolarity Oral Rehydration Solution. *JAMA* 2006;**296**:567-573

2. Mahalanabis D. Introduction of new hypo-osmolar ORS (recommended by WHO) for routine use in the management of diarrhoeal diseases a Phase IV surveillance study. Progress Report (14.2.2007).