Summary of analysis of efficacy and safety of zinc sulfate in childhood diarrhoea.

Definition
Diarrhoea is the passage of loose or watery stools at least 3 times in a 24 hour period. It is a leading cause of death among children in the developing world. Diarrhoea and malnutrition consistently rank in the top 5 causes of childhood death. 

Currently there are 2 items for diarrhoea on the WHO EML, Section 17.7 Medicines used in diarrhoea:

- 17.7.1 Oral hydration – oral dehydration salts (for glucose-electrolyte solution), powder, 20.5 g/l; and
- 17.7.2 Antidiarrhoeal (symptomatic) medicines – codeine, tablet, 30 mg (phosphate) with the footnote stating: "The public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion in the Model List will be reviewed at the next meeting of the Expert Committee."

Zinc sulfate is listed on the Anatomical Therapeutic Chemical (ATC) classification index with Defined Daily Doses (DDDs) (WHO Collaborating Centre for Drug Statistics Methodology), Oslo, Norway, 2004 under section A12 Mineral Supplements – A12C B01 Zinc sulfate.

The application for inclusion of Zinc sulphate, tablets 10mg and 20 mg is supported by clinical evidence of its superiority to placebo/no supplementation in treating or preventing diarrhoea in children.

Efficacy issues.
High level clinical evidence has accumulated proving positive effects of zinc supplementation in treating acute and persistent diarrhoea in children on standard fluid and dietary management of diarrhoea as recommended by the WHO (positive commentary of the NHS Centre for Reviews and Dissemination (CRD) of the Cochrane collaboration for the published pooled analysis).

This pooled analysis of the results of randomised controlled trials (10 trials totally) comparing Zinc supplementation (zinc sulfate 3 milligrams/kg; zinc acetate 4-5 milligrams/kg or 20 milligrams; zinc gluconate 20 milligrams) and no zinc supplementation with 1,573 participants in the zinc group and 1,513 participants in the control group included in final calculations (pooled analysis) established that zinc supplementation was effective in reducing duration and severity of acute and persistent diarrhoea.

The advantage in efficacy of zinc supplementation vs placebo or vitamin supplementation was characterised by:

- 15% lower probability of continuing diarrhoea on a given day with 95% Confidence Interval (CI): 5% to 24% in acute diarrhoea trials (3 trials);
24% lower probability of continuing diarrhoea with 95% CI: 9% to 37% in persistent diarrhoea trials (4 trials);

42% lower rate of treatment failure or death with 95% CI: 10% to 63% in persistent diarrhoea trials (4 trials);

the Relative Hazard of continuation of diarrhoea (RH) of 0.85 with 95% CI: 0.76 to 0.95 for acute diarrhoea and 0.76 with 95% CI: 0.63 to 0.91 for persistent diarrhoea (effect on recovery).

In acute diarrhoea trials no heterogeneity was detected, in persistent diarrhoea trials there tended to be greater effect of zinc supplementation in children under 12 months of age, who were male, or who had wasting or lower baseline plasma zinc concentrations.

The severity of the diarrhoea episode and safety profile of zinc supplementation were not assessed in this pooled analysis.

Numerous other randomised controlled trials support the conclusion of positive effects of zinc supplementation in treating diarrhoea in children.

Zinc supplementation in prevention of diarrhoea needs further investigation.

The latest WHO/UNICEF joint statement “Clinical Management of acute diarrhoea” outlined the findings that zinc supplementation given for 10-14 days lowers the incidence of diarrhoea in the following 2-3 months.

Safety issues
No pooled estimates exist.

Vomiting is the most commonly reported adverse reaction to zinc supplementation. Individual trials report on the lack of significant difference in vomiting between zinc supplemented children vs controls. However there are trials pointing at the increased proportion (12% increase) of children vomiting or longer duration of vomiting in zinc supplemented group.

Zinc salts inhibit copper absorption, which might be a problem in chronic overdose. In two diarrhoea trials which assessed copper status no difference was found in mean serum copper levels between zinc-supplemented and placebo-supplemented children after 14 days of supplementation. In contrast, the reduction in plasma copper levels in zinc-supplemented malnourished Pakistani children with persistent diarrhoea after 14 days of zinc supplementation (zinc sulfate 3 milligrams/kilogram/day) vs placebo suggests that caution should be exercised in supplementing severely malnourished children with zinc alone.

No published evidence on differences in effects of various zinc salts exists.

Conclusion
High quality clinical evidence has accumulated to form a convincing argument to add zinc sulfate as a new medicine for treating childhood diarrhoea, tablets, 10 milligrams; 20 milligrams on the WHO Model List of Essential Medicines.

The following addition is suggested to the proposed text for the WHO Model Formulary:

**Precautions:** excess consumption may cause severe nausea, vomiting and result in copper deficiency.


6 NHS Centre for Reviews and Dissemination; Therapeutic effects of oral zinc in acute and persistent diarrhea in children in developing countries: pooled analysis of randomized controlled trials (Structured abstract); CRD database number: DARE-20010050 In: The Cochrane Library, Issue 2, 2004. Chichester, UK: John Wiley & Sons, Ltd


14 NHS Centre for Reviews and Dissemination; Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials (Structured abstract); CRD database number: DARE-20000151; In: The Cochrane Library, Issue 2, 2004. Chichester, UK: John Wiley & Sons, Ltd


