



EMLc

ATC codes: **A12CB01**

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| Indication | Diarrhoea ICD11 code: MG31 |
| Medicine type | Chemical agent |
| List type | Core (EML) (EMLc) |
| Additional notes | * In acute diarrhoea, zinc sulfate should be used as an adjunct to oral rehydration salts |
| Formulations | Oral > Solid: 20 mg |
| EML status history | First added in 2005 (TRS 933) Changed in 2007 (TRS 950) Changed in 2011 (TRS 965) |
| Sex | All |
| Age | Also recommended for children |
| Therapeutic alternatives | The recommendation is for this specific medicine |
| Patent information | Patents have expired in most jurisdictions Read more about patents .  |
| Wikipedia | Zinc sulfate  |
| DrugBank | Zinc sulfate  |

Summary of evidence and Expert Committee recommendations

The Department of Child and Adolescent Health, WHO submitted a proposal to include a 20-mg oral dosage form of zinc sulfate, to match available products and for cost reasons. Zinc sulfate is currently listed on the EML as: Oral liquid: in 10 mg per unit dosage forms and Tablet: in 10 mg per unit dosage forms. Expert reviews were provided by Mr Andy Gray and Professor David Ofori-Adjei. The Committee noted that when zinc sulfate was originally added to the EML in 2005, only the 10-mg dosage was listed. No commercial products were then available and the basis for the listing was to ensure that 20-mg scored tablets should not be cut in half for use in infants aged less than 6 months, as this practice could not ensure that the dose of zinc administered to these infants would be precise enough. In 2010, more than 40 manufacturers are producing zinc tablets for use in the management of diarrhoea as 20-mg zinc tablets in order to reduce the cost of zinc treatment for children aged more than 6 months. Supplementing children with two 10-mg zinc tablets costs twice as much as supplementation with one single 20-mg zinc tablet. Keeping the cost of treatment as low as possible is essential to increase access to, and coverage of, the treatment. Two publications were submitted (1, 2) in support of supplementation and several additional publications were identified by the Secretariat. The main issue considered by the Committee was the safety and palatability of a 20-mg dose form for children aged less than 6 months. There is conflicting evidence on the efficacy of zinc in the subgroup of infants aged less than 6 months. A Cochrane Review stratified by age included 18 trials (13 in acute diarrhoea), of which two trials were in 1334 infants aged less than 6 months (1, 3). The review concluded that zinc reduced diarrhoea duration measured at day 3, 5, and 7 but there was significant heterogeneity. In the Cochrane Review of zinc (4) three more trials used doses higher than the currently recommended 10 mg and included some infants aged less than 6 months. The combined analysis of vomiting in trials of all infants aged less than 6 months and above, showed an increased risk of vomiting (RR 2.01; 95% CI 1.06–3.81, 1505 children, three trials). In these three trials infants received 20-mg zinc sulfate tablet (5), 15 mg zinc (6), and 20-mg zinc sulfate solution (7), respectively. The actual number of infants aged less than 6 months was not specified. The Committee considered that zinc safety is not a major issue, even given at 20 mg in infants aged less than 6 months. Zinc

administration is associated with a single reported adverse effect, vomiting, but there is no clear dose–effect relationship. Vomiting is generally limited to a single episode after the first dose in the vast majority of children. It was decided to list the flexible, dispersible 20-mg oral solid dosage form only. A palatable formulation, which could reduce the risk of vomiting, would be necessary. The Committee noted that appropriate oral liquid forms are not widely available and therefore decided to delete this dosage form.

References: 1. Brooks WA et al. Efficacy of zinc in young infants with acute watery diarrhea. *The American Journal of Clinical Nutrition*, 2005, 82(3):605–610. 2. Mazumder S et al. Effectiveness of zinc supplementation plus oral rehydration salts for diarrhoea in infants aged less than 6 months in Haryana state, India. *Bulletin of the World Health Organization*, 2010, 88(10):754–760. 3. Fischer Walker CL et al. Zinc Study Group. Zinc supplementation for the treatment of diarrhea in infants in Pakistan, India and Ethiopia. *Journal of Pediatric Gastroenterology and Nutrition*, 2006, 43(3):357–363. 4. Lazzerini M, Ronfani L. Oral zinc for treating diarrhoea in children. *Cochrane Database of Systematic Reviews*, 2008, (3):CD005436. 5. Larson CP et al. Initiation of zinc treatment for acute childhood diarrhoea, a risk for vomiting or regurgitation: a randomized double blind placebo-controlled trial. *Journal of Health, Population and Nutrition*, 2005, 23(4):311–319. 6. Bhatnagar S et al. Zinc with oral rehydration therapy reduces stool output and duration of diarrhea in hospitalized children: a randomized controlled trial. *Journal of Pediatric Gastroenterology and Nutrition*, 2004, 38(1):34–40. 7. Polat TB, Uysalol M, Çetinkaya F. Efficacy of zinc supplementation on the severity and duration of diarrhea in malnourished Turkish children. *Pediatrics International*, 2003, 45:555–559.

