A.33	Phosphorus – hypophosphatemic rickets – EMLc
Draft recommendation	☐ Recommended ☒ Not recommended (as listed by the application) Justification: I think it would make more sense to include phosphate salts for conditions associated with hypophosphatemia (see below) and not make the indication specific for hypophosphatemic rickets, a rare condition.
Does the proposed medicine address a relevant public health need?	☐ Yes ☒ No ☐ Not applicable Comments: Hypophosphatemic rickets (XLHR) is the most common cause of inherited phosphate wasting. • Incidence: 3.9 per 100,000 live births • Prevalence 4.8 per 100,000 persons Other genetic conditions are associated with phosphorus loss and require replacement as part of their management: • Autosomal dominant hypophosphatemic rickets • Hereditary hypophosphatemic rickets with hypercalciuria • Fanconi syndrome • Autosomic recessive conditions that lead to hypophosphatemia. Other conditions that can require PO phosphate supplementation: • Primary or secondary hypoparathyroidism • Renal failure, nephrotic syndrome, following kidney transplant. • Tumor induced osteomalacia. • Hyperphosphaturia after partial hepatectomy Without treatment children with XLHR develop severe and long-term complications including poor growth and long bone deformity, osteoarthritis, increased risk of fractures, dental abscesses, bone and muscle pain, stiffness, and fatigue. During adulthood, patients can develop enthesopathy, early onset osteoarthritis, hearing abnormalities, Meniere disease, and dental abscesses. Treatment should be started, before the child starts standing up.
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: Multiple small cohort studies have shown the efficacy of phosphate supplementation (in combination calcitriol). Also, additional cohort studies have shown improved outcomes if the treatment is started earlier.

Does adequate evidence exist for the safety/harms associated with the proposed medicine? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: Potential adverse events are clearly described
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Most common side effects are GI related. Patients must be monitored for: • Secondary and tertiary hyperparathyroidism • Nephrocalcinosis
Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: Hypophosphatemic rickets needs to be managed by a pediatric or adult endocrinologist. Monitoring growth, rickets, ALP, and PTH is required for those adjustments.
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☐ Yes ☒ No ☐ Not applicable Comments: There are no comparative cost and cost-effectiveness studies available. Both formulations are affordable in multiple markets.
Are there any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☒ No ☐ Not applicable Comments:

Is the proposed medicine recommended for use in a current WHO guideline? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments: Phosphate salts are recommended for the management of XLH in multiple guidelines: • European Society for Pediatric Nephrology (ESPN) • European Society for Pediatric Endocrinology (ESPE) • European Reference Network on Rare Endocrine Conditions (Endo-ERN) • European Reference Network on Rare Bone Disorders (BOND) • International Osteoporosis Foundation (IOF) Skeletal Rare Disease Working Group • European Calcified Tissue Society (ECTS) • European Pediatric Orthopedic Society (EPOS) study group on Metabolic and Genetic Bone Disorders • European Society of Craniofacial Surgery • European Society for Pediatric Neurosurgery • European Federation of Periodontology (EFP)