Phosphorus

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 18. Medicines for endocrine disorders

EMLc | ATC codes: V03AG05

Indication	Hypophosphataemic rickets ICD11 code: 5C63.22
Medicine type	Chemical agent
List type	Complementary
Formulations	**Oral > Other:** 500 mg in sachet (elemental phosphorus) granules (EMLc) **Oral > Solid > tablet:** 250 mg (elemental phosphorus) (EMLc) ; 500 mg (elemental phosphorus) (EMLc) ; 500 mg (elemental phosphorus) (effervescent) (EMLc)
EML status history	Application rejected in 2023 (TRS 1049)
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	Phosphorus
DrugBank	Phosphorus

Expert Committee recommendation

The Expert Committee noted that hypophosphataemic rickets is a rare genetic condition and the most common cause of inherited phosphate wasting that without treatment can lead to severe long-term complications. The Committee noted evidence from small cohort studies which suggested that early introduction of treatment with phosphorus and vitamin D in children with hypophosphataemic rickets had beneficial effects on growth, bone mineralization and reducing bone deformities. However, the Committee considered that hypophosphataemic rickets is a rare condition which constitutes only a small subgroup of all hypophosphataemic conditions that may benefit from phosphorus supplementation. The Committee noted that several other genetic conditions are associated with phosphorus loss and require replacement therapy as part of their management (e.g. autosomal dominant hypophosphataemic rickets, hereditary hypophosphataemic rickets with hypercalciuria and Fanconi syndrome). Other conditions that can require phosphate supplementation include primary or secondary hypoparathyroidism, renal failure, nephrotic syndrome after kidney transplant, tumour-induced osteomalacia and hyperphosphaturia after partial hepatectomy. The Expert Committee did not recommend the inclusion of phosphorus on the complementary list of the EMLc for the treatment of hypophosphataemic rickets in children at this time. The Committee considered that a comprehensive review of the evidence for phosphorus treatment across all conditions for which it is indicated should be requested for future consideration.

Background

Phosphorus has not previously been considered for inclusion in the Model Lists for management of hypophosphataemic rickets in children or any other indication.

Public health relevance

X-linked hypophosphataemia is the most common cause of inherited phosphate wasting, with an incidence of 3.9 per 100 000 live births and a prevalence ranging from 1.7 per 100 000 children to 4.8 per 100 000 population (all ages) (1). It is a progressive lifelong disease of phosphorus metabolism where renal phosphorus wasting causes abnormal bone mineralization and rickets that do not respond to vitamin D and calcium supplements. As the disease progresses, long-term complications including poor growth (long bone deformity), osteoarthritis, increased risk of fractures, dental abscesses, bone and muscle pain, and stiffness and fatigue can significantly decrease overall quality of life. Renal phosphorus wasting starts in early infancy. Skeletal manifestations become obvious later as the child begins to weight bear, when long bone deformities develop such as genu valgum or varum. Growth deceleration and rickets begin to occur during the first 2 years of life, when growth velocity is physiologically maximum.

Benefits

Treatment of hypophosphataemic rickets with phosphate salts and vitamin D has been reported to improve bone mineralization, radiographical resolution of rickets and linear growth in a number of small observational studies (2–5). A study of 11 children (10 girls, one boy, 2–12 years old) with vitamin D-resistant rickets treated with phosphate alone, or in combination with ergocalciferol or calcitriol, found that long-term use of phosphate induced mineralization of the growth plate but not of the endosteal bone surface. Long-term use of phosphate in combination with calcitriol greatly improved the mineralization of the trabecular bone (2). A study of nine children (three girls, six boys, 6 months to 16 years old) with familial X-linked hypophosphataemic rickets treated with phosphate and alfacalcidol found that combination oral therapy was effective at improving growth rate, bone histology and the radiological picture of rickets. All children had positive outcomes for healing or rickets, change in growth rate, decreased alkaline phosphatase activity and symptomatic improvements, assessed over 4–6 years (3). In a study of 24 children (15 girls, nine boys, 1–16 years old) with X-linked hypophosphataemic rickets treated with oral phosphate and calcitriol or ergocalciferol, 19 patients treated for at least 2 years before the onset of puberty had greater mean height SD score than untreated historical controls: mean difference 0.97 (95% confidence interval (CI) 0.22 to 1.75). For 13 patients who had received phosphate and calcitriol for at least 2 years, the mean change in height standard deviation (SD) score was 0.33 (95% CI 0.0 to 0.33) (4). A study of 22 adult Japanese patients (17 women, five men) with X-linked hypophosphataemic rickets evaluated the effect of combination therapy for more than 5 years with phosphate and vitamin D (as vitamin D2 or alfacalcidol) on final height (as standard deviation score). Final height of all participants was –1.69 (SD 1.11) which was significantly higher than the height at the start of treatment (–2.38 (SD 0.88)). There was no significant difference in final height in patients receiving different forms of vitamin D. The results of this study were reported to be similar to previous studies in Caucasian patients (5). Early diagnosis and initiation of treatment has been associated with improved outcomes in multiple studies (6–9).

Harms

Therapy with phosphate is associated with adverse effects that require careful monitoring and adjustment of the dosing regimen by specialist paediatricians. The most common adverse effects of oral phosphate therapy are gastrointestinal effects including abdominal discomfort and diarrhoea that can result in poor compliance with treatment (10). Secondary and tertiary hyperparathyroidism may also occur (11). Treatment-induced secondary hyperparathyroidism can be reversed by increasing calcitriol doses and reducing phosphate doses. Long-term, high-dose phosphate therapy may be an independent risk factor for tertiary hyperparathyroidism. Nephrocalcinosis (deposition of calcium in the renal parenchyma and tubules) can occur as a complication of phosphate and active vitamin D treatment, and is associated with higher doses of phosphate and/or overdose of calcitriol/alfacalcidol. Prevention is through careful dosage adjustment. Recommended safe doses have been

reported as 20–40 mg/kg a day of phosphate and 20–30 ng/kg a day of calcitriol (12). Thiazide diuretics can be used in the management of nephrocalcinosis when it occurs (13,14).

Cost / cost effectiveness

The application reported prices per 500 mg elemental phosphorus for various formulations as US$ 0.30 in India, US$ 0.68 in Mexico and US$ 0.23 in the United Kingdom. No cost–effectiveness data were presented in the application.

WHO guidelines

WHO guidelines for the management of hypophosphataemic rickets are not currently available.

Availability

Phosphate salt formulations most suitable for use in children include effervescent tablets and granules. An oral solution known as Joulie solution can be prepared by compounding pharmacists. Different formulations may be available in different markets.

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