Application for inclusion of phosphorus (phosphate salts) in the WHO Model List of Essential Medicines for children (EMLc) (April 2023)

1. Title

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To:
24nd WHO Expert Committee on the Selection and Use of Essential Medicines
World Health Organization, Geneva

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2. Summary statement of the proposal for inclusion, change, or deletion

This proposal requests the inclusion of oral phosphorus (given as phosphate salt) in the EMLc for the management of hypophosphatemic rickets (XLH) (complementary list).

The management of XLH includes phosphorus and alfacalcidol/ calcitriol. Therefore, it is important to include both medicines at the same time. Please see another application for alfacalcidol/calcitriol also submitted to the 24th WHO Expert Committee.

Management of XLH with a combination of these two affordable medicines can prevent poor growth, rickets and debilitating complications that require surgical management.

Phosphate metabolism

Phosphorus is one of the most abundant elements in the human body and plays a crucial role in many cellular functions like nucleotide and energy metabolism, maintenance of acid-base balance, cell signalling, and cell membrane integrity, in addition to bone mineralization. A major fraction (85%) of total body phosphorus is stored in the skeletal system, with only 1% in the extracellular fluid, the remainder in the soft tissues, and red blood cells (1).

Any clinical condition inducing chronic hypophosphatemia leads to vitamin D resistant rickets in children. Rickets is a disease of growing bones occurring due to poor mineralization of growth plates causing delayed and erratic chondrocyte apoptosis. The classic features are epiphyseal widening, metaphyseal cupping and fraying on radiographs, and osteopenia of the diaphysis of long bones. The weakened long bones can bend on weight-bearing which creates the classic sign of bowed legs (rev in 2).

Hypophosphatemic rickets

The commonest cause of XLH in children is X-linked hypophosphatemic rickets, a genetic condition involving the PHEX gene located on chromosome Xp22.1 and expressed predominantly in bone and teeth. PHEX mutation causes abnormal fibroblast growth factor 23 (FGF-23) regulation (2,3). FGF-23 has a phosphaturic effect on proximal renal tubules. Its concentration is elevated in XLH and, as a consequence, cause a decrease in serum phosphorus which is a physiological stimulus for 1,25-vitamin D production. In addition, FGF-23 decreases synthesis and increases catabolism of 1,25-Vitamin D.

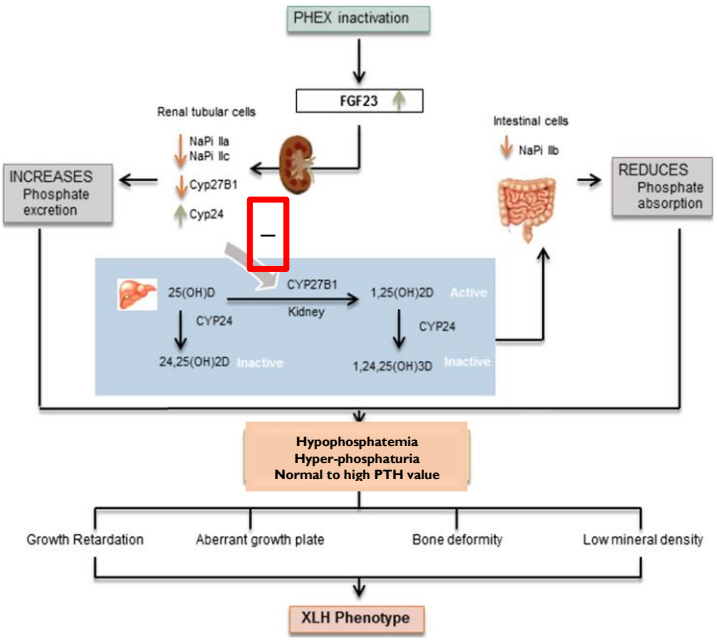

Figure 1: Modified from reference (4)

Management therefore involves careful balancing of phosphate therapy (using frequent dosing of soluble phosphate) and vitamin D analogues, in the form of calcitriol or 1-

alfacalcidol (see other application to the 24th WHO Expert Committee). Inadequate balancing of these two components leads to failure to heal the rickets or can lead to calcium deposition in the kidneys and impaired renal function. For young children, a liquid form of an active vitamin D compound is essential (currently this is 1-alfacalcidol) while for older patients access to capsules of calcitriol or 1-alfacalcidol is essential for dose adjustments.

3. Consultation with WHO technical departments

No WHO department was consulted. In 2019, the WHO published a detailed document on "Nutritional rickets: a review of disease burden, causes, diagnosis, prevention and treatment" (5). To our knowledge, in contrast to the most common form of rickets (Vit D deficient rickets), no WHO department has proposed guidelines for conditions associated with resistance to Vitamin D such as hypophosphatemic rickets.

4. Other organizations consulted and/or supporting this submission

This submission is part of a larger project by a group of endocrinologists with worldwide representation who met regularly for 12 months (2020-2021) with the goal of performing an in-depth review of the essential medicines included in Section 18. of the EML and the EMLc ("Medicines for endocrines disorders"). The group included both adult and pediatric endocrinologists: Drs. Chanoine (Canada) and Molitch (USA) (co-Chairs) and Drs. von Oettingen (Canada), Villarroel (Bolivia), Kalra (India), Paulose (India), Abodo (Ivory Coast), Ramaiya (Tanzania), Donaghue (Australia), Junfen Fu (China) and de Beaufort (Luxembourg). In addition, we worked with economists (Drs. Ewen and Beran from Switzerland), pharmacists (Miss. Kavanagh and Dr Gray from UK and Karekezi from Kenya) and a dietitian (Dr. Besancon from Mali). This application is led by Global Pediatric Endocrinology and Diabetes (GPED) and the International Society of Endocrinology (ISE).

We are at a time when capacity in pediatric endocrinology is increasing fast in resource limited settings and when expertise becomes much more available. Members of the International Consortium for Pediatric Endocrinology and Diabetes (see letter of support) are proud of these developments and, in parallel, are working hard to make the essential medicines relevant to our speciality available to patients.

This submission is supported by Global Pediatric Endocrinology and Diabetes (GPED, letter of support #a), by the International Consortium for Pediatric Endocrinology and Diabetes (ICPE, letter of support #b), by the Endocrine Society (Letter of support #c) and by the XLH network (letter of support #d). The XLH network is a worldwide patient support organization for people living and dealing with X-linked hypophosphatemia (XLH) (https://www.xlhnetwork.org/). Importantly, the letter of support from the XLH network highlights the importance of having both phosphorus and alfacalcidol/calcitriol added to the EML/EMLc because both medicines are an integral part of the treatment of X-linked hypophosphatemic rickets.

5. Key Information for the Proposed Medicines

Phosphorus as the chemical entity is formulated into a variety of phosphate salt forms that permit the administration of the medicine. The most commonly available product are potassium phosphate and sodium phosphate. Each of these salt forms are available in differing chemical formulations. From a disease management point of view, any of the products can be used provided that the amount of elemental phosphorus is taken into account by the prescriber.

International non-proprietary name (INN) of the proposed Medicines

To our knowledge, there is no INN for phosphate salts. The Unique Ingredient Identifier code has been offered as an alternative.

Phosphate UNII: NK08V8K8HR
Potassium Phosphate UNII: B7862WZ632
Monobasic Potassium Phosphate UNII: 4J9FJ0HL51
Dibasic Potassium Phosphate UNII: CI71S98N1Z

Monobasic Sodium Phosphate UNII: 3980JIH2SW (Note there are several hydration status available for this salt form. Each hydration status has an independent UNII):
Monobasic sodium phosphate monohydrate: 593YOG76RN
Monobasic sodium phosphate dihydrate: 5QWK665956
Anhydrous monobasic sodium phosphate: KH7I04HPUU

Dibasic Sodium Phosphate : Note there are several hydration status available for this salt form. Each hydration status has an independent UNII
Anhydrous dibasic sodium phosphate 22ADO53M6F
Dibasic sodium phosphate heptahydrate 70WT22SF4B
Dibasic sodium phosphate dihydrate 94255I6E2T
Dibasic sodium phosphate dodecahydrate E1W4N241FO
Dibasic sodium phosphate GR686LBA74
Sodium phosphate SE337SVY37

Anatomic therapeutic chemical (ATC) code of the proposed medicine

A06AD17, A06AG01, B05XA09 and V03AG05 all code for sodium phosphate. However, the indications (constipation, enema, IV treatment) are not relevant to the present submission.

Dibasic Sodium Phosphate ATC code: A06AD17; A06AG01; B05XA09

Monobasic Sodium Phosphate ATC code: A06AD17; A06AG01

A review of Martinadale (complete drug reference) did not identify any ATC for potassium phosphate.

Indication

5C63.22 (X-linked) Hypophosphatemic rickets

6. Proposal for an individual medicine or representative of a pharmacological class/therapeutic group

Individual medicine (phosphate salt).

Suggested wording

Phosphorus is available as tablets of sodium phosphate, potassium phosphate or a combination of both salts. These tablets are then usually diluted in liquid to be taken orally by the patient.

Phosphorus is a mineral and could belong to section 27. VITAMINS AND MINERALS of the EMLc. However, the present submission focuses on phosphorus as an essential medicine in

medical conditions characterized by phosphorus loss. As such, we suggest that phosphorus be part of a new subsection on “diseases of bone and calcium metabolism” within section 18. MEDICINES FOR ENDOCRINE DISORDERS.

Please see two other submissions targeting disorders of calcium and bone metabolism (biphosphonates and calcitriol/alfacalcidol).

XLH is usually managed by a specialist (pediatric or adult endocrinologist). Thus, we propose that phosphorus be included in the complementary list.

18. MEDICINES FOR ENDOCRINE DISORDERS	
18.1 Diseases of bone and calcium metabolism	
Complementary list	
Phosphorus	**Tablets:** Potassium phosphate and sodium phosphate alone or in combination (250 and 500 mg of elemental phosphorus)

7. Information supporting the public health relevance

Epidemiological information on disease burden

XLH 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 persons (children and adults) (6).

Other genetic conditions associated with phosphorus loss:

- Rare forms of autosomal dominant (ADHR) (7) and autosomal recessive (ARHR) forms have been reported.
- Hereditary hypophosphatemic rickets with hypercalciuria (HHRH) is an autosomal recessive disorder caused by mutations in SLC34A3 that encodes sodium-phosphate co-transporter on the renal proximal tubules. In contrast to XLH, the affected patients have 1,25-vitamin D levels that are appropriately elevated for the low serum phosphate. This leads to increased intestinal absorption of both phosphate and calcium leading to hypercalciuria and suppressed PTH, and increased risk of nephrocalcinosis. These patients are treated only with phosphate salts. Treatment with active vitamin D analogues can worsen hypercalciuria in these patients (6).
- Fanconi Syndrome is a generalized proximal tubulopathy seen in some autosomal recessive diseases (e.g., cystinosis, Lowe syndrome, tyrosinosis) and in X-linked recessive Dent's disease. Proximal tubular solute wasting causes aminoaciduria, hypercalciuria, and phosphaturia, with or without bicarbonaturia, and can present with rickets and osteomalacia.

Target population(s)

All children with XLH from the time they become weight-bearing (first year or life) till the end of longitudinal growth. In adults with XLH, phosphorus supplementation is sometimes provided for bone pain.

Alternative medicines currently included on the Model Lists for the proposed indication(s)

Phosphorus (given as phosphate salts) and vitamin D analogues (calcitriol or 1-alfacalcidol) were the only approved medicines until recently. Calcitriol and 1-alfacalcidol are the focus of another submission to the 2023 EML (see other EML submission).

In 2018, the United States FDA and the European EMA approved burosumab, an anti FGF-23 monoclonal antibody for the treatment of XLH in children aged 1 year and above (reviewed in 6). Burosumab was demonstrated to be safe and efficacious in a randomized, multicenter, open-label clinical trial in 61 children 1 to 12 years of age with XLH and moderate to severe rickets despite treatment with phosphate and calcitriol (8). Adverse effects were minimal, except for an increase in the incidence of dental abscesses. However, burosumab is not yet used as a first-line treatment in patients with XLH. A registry is ongoing to gather more longitudinal information on this treatment. Its high price (> 100,000 USD/year) makes it unaffordable for many countries, including HIC countries such as New Zealand where it is not available. Cost-effectiveness studies are ongoing. In addition, Burosumab may not be required for mild forms of XLH that have been shown to respond very well to phosphorus and vit D analogs. **Burosumab is NOT the focus of this submission.**

8. Treatment details

XLH 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. It is followed in specialized centers where a pediatric endocrinologist or a pediatrician with expertise in rickets is available.

As the disease progresses, long-term complications including poor growth (long bone deformity), osteoarthritis, increased risk of fractures, dental abscesses, bone and muscle pain, stiffness, and fatigue significantly decrease the overall quality of life (9,10). During adulthood, patients can develop enthesopathy, early onset osteoarthritis, hearing abnormalities, Meniere disease, and dental abscesses.

Dosage regimen and duration of treatment

Early initiation of treatment with phosphorus and calcitriol/alfacalcidol, has been shown to optimize growth, improve bone mineralization and prevent and/or reduce bone deformities (11) (Reviewed in Table 1). Continued management in adulthood helps to sustain the positive effects acquired from childhood treatment (12).

In XLH, renal phosphorus wasting starts in early infancy. However, skeletal manifestations become obvious only later as the toddler learns to weight bear when long bone deformities like genu valgum or varum develop. Growth deceleration and rickets in XLH begin to occur during the first 2 years of age when the growth velocity is physiologically maximum. Therefore, early initiation of treatment is essential, before the child starts standing up and certainly prior to 18 months of age, and before the overt manifestation of rickets develops.

ADHR is rare and is also FGF-23 mediated. It is inherited with variable penetrance and hence has a variable phenotype. The severity of renal phosphate wasting can wax and wane. Clinical presentation is similar to XLHR in early childhood although some may present with a milder disease with preserved stature in later life (7).

ARHR is another rare inherited hypophosphatemic rickets presenting similarly to XLH. A few of these children have inactivating mutations of the ENPP1 gene that cause rickets which is not mediated by FGF-23.

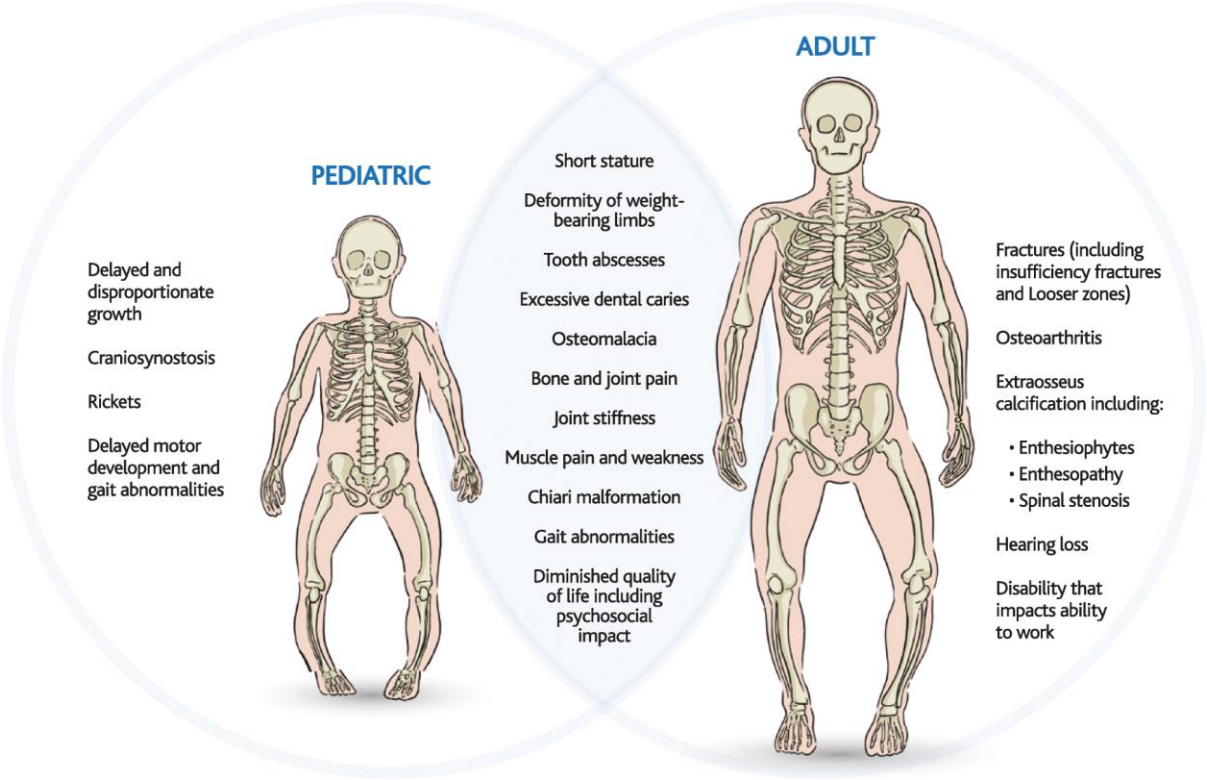

Figure 2: Symptomatology and pathophysiology of XLH. The signs, symptoms, sequelae, and long-term consequences of XLH in paediatric (left) and adult (right) patients.From Beck-Nielsen et al,(10).

Diagnosis:

A diagnosis of XLH should be considered in any child with clinical and/or radiological signs of rickets, impaired growth velocity, and low serum phosphate levels with renal phosphate wasting, in the absence of vitamin D or calcium deficiency.

Evaluation includes:

- Clinical examination for evidence of rickets, growth failure, dental abnormalities, and signs of craniosynostosis and/or intracranial hypertension
- Radiological evaluation to diagnose and grade rickets and osteomalacia
- Biochemical tests: Serum phosphate, calcium, alkaline phosphatase (ALP) and creatinine, and spot urine phosphate and creatinine for calculation of the tubular maximum reabsorption of phosphate per glomerular filtration rate (TmP/GFR) and urinary calcium: creatinine ratio (included in the Essential Diagnostics List). When available, parathyroid hormone (PTH) (submitted for inclusion in the 4th Essential Diagnostics List), 25(OH) vitamin D, 1,25- Vitamin D are helpful. If these tests are not available, the absence of rickets healing in a child with low phosphorus despite appropriate supplementation in Vit D will inform the clinical diagnosis of XLH.
- Diagnosis of XLH can be confirmed by genetic analysis of the PHEX gene where possible. In the absence of genetics, elevated plasma levels of intact FGF23 and/or a positive family history of XLHR will support the diagnosis. These determinations, often not available, even in many high resource countries, do not affect the decision of treating XLH.

Treatment:

The conventional treatment of XLH is essentially oral replacement of phosphorus and calcitriol/alfacalcidol (8,13–16). In HHRH only phosphorus is used (17)

In XLH, a combination of oral phosphate salts and active vitamin D is recommended as soon as the diagnosis is made. In infants and children, elemental phosphorus is given at a starting dose of 20-60 mg/kg/d, divided into 4-6 doses spread over 24 hours. This dose is later adjusted according to improvement in growth, rickets, ALP, and PTH. Once ALP normalizes, the frequency of phosphorus administration can be reduced to 3-4 times per day. Typically, a lower dose is sufficient in milder phenotypes. But, in cases with poor response, the dose can be progressively increased up to 80 mg/kg/d. Dose reduction is needed in case of adverse effects like gastrointestinal discomfort or hyperparathyroidism.

The initial dose of active Vitamin D is 20-30 ng/kg/d of calcitriol or 30-50 ng/kg/d of 1-alfacalcidol. An empirical dose of 0.5mcg calcitriol or 1mcg 1-alfacalcidol can be started in children older than 1 year and titrated later (18,19).

Routine supplementation of cholecalciferol supplements is recommended, similar to any child. Calcium supplementation is not routinely needed as long as daily dietary calcium recommendations are met.

The typical preparation available is the sodium phosphate effervescent tablet, which contains the equivalent to 500mg of phosphorous per tablet. A one-year-old child typically weighing 9kg would need a total daily dose of 180-540mg daily. For an average 12 years old of 39kg this would be 2,340mg/day and a 14 year child weighting 50kg this equates to 3000mg per day.

Follow-up and monitoring:

The frequency of follow-up depends upon the clinical picture. Children with hypophosphatemic rickets should be followed up once every 3 months during the initial phase of treatment and during periods of rapid growth (under 5 years, during puberty). Thereafter, this can be reduced to once every 6 months for those who respond well to therapy and are in stable condition. Follow-up is essentially clinical with simple chemistry and radiological examinations to assess the response to therapy. Additional tests (PTH, renal ultrasound) are important to monitor the safety of the patients, at a frequency adapted on an individual basis.

Clinical assessment:

- Anthropometry: Measure and plot weight, height, head circumference under 5 y age, and body mass index every visit. Changes in intercondylar and intermalleolar distances should be documented where possible. Beyond 5 y age, bone age assessment helps to evaluate growth potential.
- Twice-yearly blood pressure should be measured and if it is persistently >95th percentile, an echocardiogram should be done.
- If lower limb deformity is evident, annual orthopedic evaluation is needed.
- Annual hearing screen for those older than 8 years and twice-yearly dental visits after tooth eruption

Biochemical assessment:

- Serum calcium, phosphate, ALP and creatinine at each visit
- Urine calcium creatinine ratio every 6 months
- PTH (submitted to the 4th EDL in 2022) is important when hyperparathyroidism, a known complication of the treatment, is suspected.

- 25(OH)Vitamin D once a year (if available and clinically indicated)

Radiological assessment:

- As clinically indicated for leg deformities)
- Renal ultrasound is recommended yearly in those with nephrocalcinosis, and once in 2 years in those without. If skull morphology is suggestive of craniosynostosis, MRI brain, fundoscopy and neurosurgical consultation are needed

Requirements to ensure appropriate use of the medicine(s)

Patients with XLH (and other less common forms) should be followed by paediatricians and pediatric subspecialists. Pediatric endocrinologists are commonly those managing these patients. As such, the medicines should be included in the complementary list of the EMLc. Safety of the medicine s directly dependent on the dosage (see below).

Recommendations in existing WHO guidelines

Not available

Recommendations in other current clinical guidelines

Detailed evidence-based guidelines have been recently published in Nature Reviews/ Nephrology by an international group of 20 pediatricians and pediatric subspecialists (19). The above recommendations are in line with these guidelines. The guidelines were endorsed by the following societies:

- 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)

9. Review of benefits: Summary of comparative effectiveness

Treatment of hypophosphatemic rickets with phosphate salts and active vitamin D has been shown to improve bone mineralization, radiographic resolution of rickets and in many studies over the last 50 years (13,20–24) and is better with early diagnosis and initiation of treatment (11,25–27).

Table 1. List of a few studies reporting the effects of conventional treatment of HHR with phosphate and active Vitamin D.

Author, year, and aim of the study	Methods	Results	Conclusions
Glorieux F et al. (13) 1972	8 children with XLHR (3 girls, 5 boys, 3-15 years of age) were treated for a total of	Resolution of radiographic evidence of rickets and acceleration of growth in all and correction of	Acceleration of growth and resolution of

Use of Phosphate and Vitamin D to Prevent Dwarfism and Rickets in XLHR	11,297 patient days with phosphorus and vitamin D2	dwarfism in 3 female and 2 male subjects	radiological rickets
Glorieux F et al. (20) 1980 Bone response to phosphate and calcitriol in Vitamin D-resistant rickets	11 children with vitamin D-resistant rickets with a phosphate mixture either alone or with ergocalciferol or calcitriol. Bone changes analysed by radiology and bone histomorphometry	Phosphate induced mineralization of the growth plate but not of the endosteal bone surface. Combined calcitriol and phosphate greatly improved the mineralization of trabecular bone.	Combined calcitriol and phosphate regimen is useful in the treatment of vitamin D-resistant rickets.
Rasmussen H et al. (21) 1981 Long-term treatment of HHR with phosphorus and active vitamin D	9 children with HHR were treated with oral phosphate and active Vitamin D and followed up for 4-6 years	All nine had positive responses as judged by healing of rickets, change in growth rate, decrease in ALP, and symptomatic improvement. Phosphate and active Vitamin D doses need to be balanced to avoid hypercalciuria and secondary hyperparathyroidism.	Combined treatment with active Vitamin D and oral phosphate is an effective form of therapy for HHR.
Verge C et al. (22) 1991 Effect of therapy in XLHR	24 patients with XLHR (9 boys & 15 girls aged 1 to 16 years were treated with phosphate and calcitriol for a duration of 0.3 to 11.8 years	Patients treated for at least two years before the onset of puberty (n = 19) had a mean height SDS of -1.08, as compared with -2.05 in the untreated historical controls. The 13 patients who had been treated with calcitriol and phosphate for at least two years had an increase in the mean height SD score of 0.33, from -1.58 to -1.25 (95% CI: 0 to 0.67; P = 0.05).	Therapy with calcitriol and phosphate may increase the growth of children with XLHR
Petersen D et al. (23) 1992 XLHR: A Study of Linear Growth Response to Calcitriol and Phosphate Therapy	15 patients with family history of XLHR and 5 sporadic cases were treated for 3 years. 12 were good growers (height velocity > mean) and 8 were poor growers (height velocity < mean).	No difference in mean age, dietary calcium, calcitriol dose or compliance, or Pi dose or compliance. The TmP/GFR of the good growers improved with therapy (1.9 f 0.2 to 2.6 f 0.2 mg/dl, p = 0.01), and their posttreatment value	The findings suggest that calcitriol may exert a direct effect on the renal tubule to improve Pi reclamation in XLH

	Data from these 2 groups is contrasted.	was higher compared to that of the poor growers	
Miyamoto J et al. (24) 2000 To report adult height and therapeutic effect of phosphate and Vitamin D on final height in patients with XLHR.	22 Japanese participants (5 males, 17 females) treated with phosphate and vitamin D (vitamin D2 or 1alpha-hydroxyvitamin D3) for more than five years	Final height for all participants was -1.69+/-11.11 SDS. This was significantly higher than height at the initiation of treatment (-2.38+/-0.88 SD) for all participants (P<0.01).	Combination therapy of vitamin D and phosphate improved final height of Japanese patients with XLHR as is similar to previous Caucasian studies.
Mäkitie, O et al. (25) 2003 To assess whether age at treatment onset impacts the outcome in patients with XLHR	Retrospective Growth data, biochemistry, and radiographs of 19 well-controlled patients with XLHR were analyzed. Patients were divided into two groups based on the age at treatment onset (group 1, <1.0 yr; group 2, ≥1.0 yr).	The median height z-score was higher in group 1 (n = 8) than in group 2 (n = 11) at treatment onset [-0.4 SDS vs. -1.7 SDS; P = 0.001], at the end of the first treatment year (-0.7 SDS vs. -1.8 SDS; P = 0.009), throughout childhood (P > 0.05) and until predicted adult height (-0.2 SDS vs. -1.2 SDS; P = 0.06). Radiographic signs of rickets were more marked in group 2, but significant even in group 1.	Treatment commenced in early infancy results in improved outcome in patients with XLHR, but does not completely normalize skeletal development.
Ariceta G et al. (26) 2007 Linear growth in XLHR	27 children with XLHR (20 girls, 7 boys) were studied at 10.12 years of age (1.58-18.56). All received oral treatment with phosphate and calcitriol.	After 5 years' follow-up, Z-height was -0.91 (- 4.56; 0.17), not different from that at baseline (P = 0.465). Eight patients had a Z-height </= -2SD at the last visit. Impaired linear growth was associated with age >2 years at diagnosis, male gender, and non-adherence to treatment.	Linear growth failure appeared in a third of XLHR children. Efforts need to be made to reduce the age of diagnosis and to improve adherence to treatment.
Quinlan C et al. (27) 2012 Growth in PHEX-associated XLHR: the importance of early treatment	Efficacy of calcitriol and phosphate therapy on longitudinal growth in relation to age at treatment onset. A single-center review of children with XLHR and documented PHEX mutations.	Recent HSDS was significantly (p = 0.009) better in G1 [-0.7 (-1.5 to 0.3)] vs G2 [-2.0 (-2.3 to -1.0)]. No effects of gender or genotype on growth could be identified. Children with PHEX-associated XLHR benefit from early treatment and	Our findings emphasize the importance of early diagnosis to allow treatment before growth has been compromised.

	Divided into 2 groups based on age at onset of treatment. G1 (N=10): <1 y; G2 (N=13): >1 y.	can achieve normal growth. Minimal catchup growth was seen in those who started treatment later.	
Cagnoli M et al. (11) 2017 Spontaneous Growth and effect of early therapy with calcitriol and phosphate in XLHR	Size at birth and all-time lowest Height SDS (r=0.56 p=0.002) are correlated as well as all-time low HSDS and last height during puberty (r=0.62 p=0.001). A cohort of 18 treated patients was compared to untreated patients. 10 of 18 patients were treated before the age 18 months.	Height at diagnosis decelerates until a mean age of 4.3 y to a nadir (-3.2 HSDS). A spontaneous catch-up growth (+1.3 HSDS) occurs until start of puberty. In those with treatment onset <18 months, mean HSDS decelerates to -2.2 SDS at age 4.4 y. and increases to -1.4 SDS at age 9.9 years. Adult height was -2.4 HSDS.	untreated children with XLR have normal length at birth, diminished growth rate compared to reference children until 4.3 years and spontaneous catch-up growth of 1.3 HSDS until start of puberty. Improved growth rate occurs with treatment onset before 18 months.
Sochett E et al. (28) 2004 This study assessed whether pubertal growth and metabolic control contribute to the height deficit.	Includes patients with XLHR who were treated with Phosphate and calcitriol from diagnosis to adult height; their hospital records, biochemistry and radiographs were reviewed.	6 females with XLHR were included. Their mean peak height velocity and total height gain during puberty were nearly normal despite deteriorating metabolic control.	In treated girls with XLHR, the pubertal growth is nearly normal despite suboptimal metabolic control. The major height loss occurs prior to puberty and is not recovered during the pubertal growth spurt.
Alikasifoglu A et al. (29) 2021 Exploring genotype and phenotypic spectrum XLHR, focusing on short-term, long-term, and pubertal impact of conventional treatment	Observational 16 patients from 12 unrelated families with XLHR	Median adult height was lower than median height on admission (-3.8 and -2.3 SDS, respectively), slightly better in compliant patients (-2.6 vs. -3.7 SDS, respectively), metabolic and radiographic recovery were not achieved, adherence was low (30%).	Conventional treatment appears to have limited effect on metabolic, clinical and radiographic recovery in XLHR.

The effect of conventional therapy with phosphorus and alfacalcidol/calcitriol is directly related to the compliance with the treatment (28,29).

10. Review of harms and toxicity: summary of evidence on safety

Phosphate and calcitriol treatment in hypophosphatemic rickets has made a tremendous difference in the quality of life of affected children. However, therapy with phosphate is associated with adverse effects (AE) that demand careful monitoring and adjustment of the dosing regimen by specialist pediatricians. The AE can be gastrointestinal, parathyroid related, or renal.

Gastrointestinal: Most common side effects of oral phosphate therapy are abdominal discomfort and diarrhoea that can cause poor compliance with medication (30).

Secondary hyperparathyroidism (SHPT): Different factors contribute to SHPT which happens relatively frequently with phosphate therapy (31). Treatment-induced SHPT in patients with XLHR can be reversed by increasing calcitriol doses and reducing phosphate doses.

Tertiary hyperparathyroidism (THPT): Prolonged unchecked SHPT can lead to parathyroid hyperplasia and THPT. Long-term, high-dose phosphate therapy may be an independent risk factor for this rare and serious complication (31).

Nephrocalcinosis: Nephrocalcinosis is a complication of XLH treatment. It is due to higher doses of phosphate and/or overdosage of calcitriol/alfacalcidol. This complication can be prevented by careful adjustment of the phosphorus and the alfacalcidol/calcitriol. For prevention, a safety phosphate dose of 20-40 mg/kg/d and calcitriol dose of 20-30 ng/kg/d is recommended. (32) Thiazide diuretics can halt the progression of nephrocalcinosis once it occurs (33,34).

11. Summary of available data on comparative cost and cost-effectiveness

To our knowledge, there is no comparative cost and cost-effectiveness studies on the treatment of XLH with phosphate and alfacalcidol/calcitriol.

It is important to note that both medicines are affordable:

India: Addphos sachet (500mg elemental phosphorus): 24.50 INR **(= 0.3 USD)**.

UK: Phosphate Sandoz effervescent tablets (Sodium dihydrogen phosphate anhydrous, 500 mg elemental phosphorus): Drug Tariff (Part VIIIA Category C): 0.194 Pound **(=0.23 USD)**

Mexico: (500mg elemental phosphorus): 13 pesos **(= 0.68 USD)**

12. **Summary of the regulatory status of medicine** (35–40)

Country	**Form and elemental phosphorus**	**Type of phosphorus salt**
Australia	Effervescent Tablet, 500mg	Sodium phosphate
USA	Film-coated Tablets, 250mg	A combination of sodium phosphate and potassium phosphate
Canada	Effervescent tablet, 500mg Clear liquid, 125mg/ml	Sodium phosphate
UK	Effervescent Tablet, 500mg	Sodium Phosphate
India	Granules, 500 mg/sachet Effervescent Tablet, 500mg	Sodium acid phosphate
Pakistan	Joulie's solution (1mmol/ml)	Sodium phosphate

13. Availability of pharmacopeial standards (British pharmacopeia, International pharmacopeia, European pharmacopeia, Unites States of America pharmacopeia)

The varying salt forms and hydration status of the phosphate salts leads to complex picture of the pharmacopeial standards. The individual pharmacopeia may specify one or more status, although not all will be represented in any single pharmacopoeia.

	International Pharmacopoeia	United States Pharmacopoeia	European Pharmacopoeia	British Pharmacopoeia	Japanese Pharmacopoeia
Monobasic Potassium Phosphate		Yes	Yes		
Dibasic Potassium Phosphate		Yes	Yes		
Monobasic Sodium Phosphate		Yes As Monobasic Sodium Phosphate	Yes As Sodium dihydrogen phosphate dihydrate)	Yes As Sodium Dihydrogen Phosphate and Sodium Dihydrogen Phosphate Monohydrate	
Dibasic Sodium Phosphate		Yes As Dibasic Sodium Phosphate	Yes As Disodium Hydrogen Phosphate		
Tribasic Sodium Phosphate		Yes			

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