HYPOPHOSPHATASIA (HPP)

ALEXION®
AstraZeneca Rare Disease

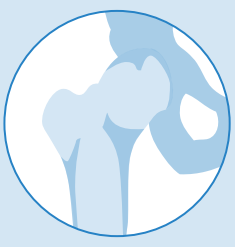
WHAT IS HYPOPHOSPHATASIA?

Hypophosphatasia (HPP) is a **rare, genetic (inherited), metabolic disease** characterized by **impaired mineralization ("calcification")**, the process that hardens and strengthens bones and teeth.[1,2]

This can lead to poor growth and development, weakness and deformity of bones and other skeletal abnormalities, and premature loss of teeth with the root intact. **As a result, the disease can have a debilitating impact, including loss of physical function.**[1,3]

HPP is caused by a defect in the gene that is responsible for making an enzyme known as **alkaline phosphatase (ALP)**, which is important for building healthy bones.[1,4]

HEALTHY BONE



When ALP functions normally, it allows calcium and phosphate to bind together to **form healthy, strong bones**.[4,5]

BONE IMPACTED BY HPP

In people with HPP, ALP levels are low, which can **prevent proper bone development** and can **cause calcium and phosphate to build up in other places throughout the body, damaging organs.**[3]

The severity of HPP can be wide-ranging and may present in many different ways.

HPP can **affect males and females of all ages.**[1]

When signs and symptoms are present **before 6 months of age**, HPP is referred to as **perinatal/infantile-onset and can be fatal.**[1]

All patients, including those whose signs or symptoms are not recognized until childhood or adulthood, may experience **significant disease burden that impacts their daily life**, including the ability to perform daily tasks or walk.[1]

SIGNS AND SYMPTOMS MAY VARY AND CAN IMPACT MANY DIFFERENT PARTS OF THE BODY, INCLUDING:[1,2,6-9]

Bones
(abnormally shaped head*, bone deformities, frequent fractures, persistent bone pain)

Muscles and joints
(muscle weakness, fatigue, arthritis)

Ribs and lungs
(underdeveloped ribs and lungs*, severe breathing difficulties*)

Central nervous system
(Vision loss, seizures*)

Kidneys
(kidney stones, decreased kidney function)

Teeth
(early tooth loss with the root intact, gum disease)

New symptoms can appear at **any age and worsen over time**, causing significant **disability or life-threatening complications**.

*Symptoms normally seen in infants and/or young children

HOW IS HPP DIAGNOSED?

Since HPP shares symptoms with other, more common diseases, **it can be misdiagnosed, and diagnosis is often delayed.**[1, 10]

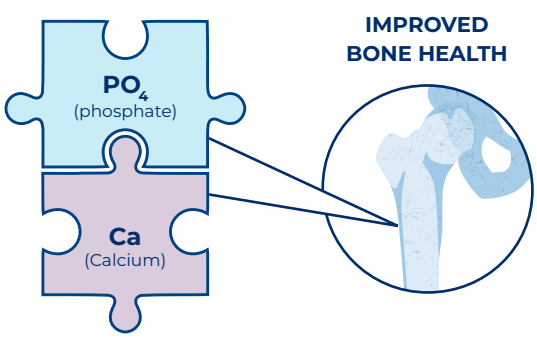
Once a person shows signs and symptoms of HPP, **a full clinical assessment and blood test** for low ALP can help lead to a correct diagnosis. **Genetic testing** may also be helpful in confirming HPP.[11]

HPP is a lifelong disease, so an **early diagnosis is critical** to ensure appropriate disease management.[11]

HOW HAS HPP TREATMENT EVOLVED?

Initially, treatment for HPP relied only on supportive care and symptom management, but research has led to more options.

Clinical studies in HPP have shown that replacing deficient ALP can improve the body's ability to mineralize bone by allowing **phosphate and calcium to bind together**. This has proven **to improve bone health and mobility, as well as survival in infants.**[12]



Alexion's leadership in rare disease led to the **first and only approved medicine** to treat the underlying cause of HPP for patients with **signs and symptoms of the disease during childhood.**

HOW IS ALEXION CONTINUING TO INNOVATE FOR HPP PATIENTS?

We continue to **innovate for patients with HPP and accelerate the development of life-changing therapies.**

Alexion is progressing our next generation alkaline phosphatase enzyme replacement therapy in clinical trials in adults and children with HPP, with the intention of **uncovering new ways to improve the patient experience and provide additional treatment options** to help more people living with this devastating disease.

References:

1. Rockman-Greenberg C. (2013). Hypophosphatasia. *Pediatric endocrinology reviews: PER, 10 Suppl 2*, 380–388.
2. FRASER D. (1957). Hypophosphatasia. *The American journal of medicine, 22*(5), 730–746.
3. Beck C, et al. (2009). Hypophosphatasia —recent advances in diagnosis and treatment. *The Open Bone Journal*; 1:8-15.
4. Whyte MP. (2008) Hypophosphatasia: nature's window on alkaline phosphatase function in humans. *Principles of Bone Biology, Academic Press*; 2008:1573-1598.
5. Whyte M. P. (2010). Physiological role of alkaline phosphatase explored in hypophosphatasia. *Annals of the New York Academy of Sciences*, 1192, 190–200.
6. Whyte MP, et al. (2019). Natural History of Perinatal and Infantile Hypophosphatasia: A Retrospective Study. *The Journal of Pediatrics*. 209, 116–124.e4.
7. Weber TJ, et al. (2016). Burden of disease in adult patients with hypophosphatasia: Results from two patient-reported surveys. *Metabolism: clinical and experimental, 65*(10), 1522–1530.
8. Beck C, et al. (2011). Whole-body MRI in the childhood form of hypophosphatasia. *Rheumatology international*, 31(10), 1315–1320.
9. Leung EC, et al. (2013). Outcome of perinatal hypophosphatasia in manitoba mennonites: a retrospective cohort analysis. *JIMD reports*, 11, 73–78.
10. Mohn A, et al. (2011). Hypophosphatasia in a child with widened anterior fontanelle: lessons learned from late diagnosis and incorrect treatment. *Acta paediatrica* (Oslo, Norway: 1992), 100(7), e43–e46.
11. Mornet, E., & Nunes, M. E. (2016). Hypophosphatasia. *GeneReviews®. University of Washington, Seattle*.
12. Magdaleno AL, et al (2019). ADULT-ONSET HYPOPHOSPHATASIA: BEFORE AND AFTER TREATMENT WITH ASFOTASE ALFA. *AACE clinical case reports, 5*(6), e344–e348.