**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Highly Specialised Technologies Evaluation**

# Asfotase alfa for treating paediatric-onset hypophosphatasia (review of Highly Specialised technologies guidance 6)

**Final scope**

## Remit/evaluation objective

To evaluate the benefits and costs of asfotase alfa within its marketing authorisation for treating paediatric-onset hypophosphatasia for national commissioning by NHS England.

## Background

Hypophosphatasia is a genetic disorder caused by mutations in the *TNSALP* gene which reduce the activity of the enzyme tissue nonspecific alkaline phosphatase. Over 375 different mutations of this gene leading to hypophosphatasia have been identified. The reduction of this enzyme's activity disrupts mineralisation, a process in which calcium and phosphorous are deposited in developing bones and teeth. This leads to ricket-like symptoms, softening and weakening of the bones (osteomalacia), bone deformity and a greater incidence of fractures. Fractures are particularly common in adults but less common in children. Hypophosphatasia can also lead to generalised seizures because of vitamin B6 deficiency, as well as renal and respiratory complications.

The signs and symptoms of hypophosphatasia vary widely and can appear anytime from before birth to adulthood. Six clinical forms are currently recognised: perinatal (lethal), perinatal (benign [non-lethal]), infantile (where symptoms start within 6 months after birth), childhood, adult, and odontohypophosphatasia (which only affects the teeth). The most severe hypophosphatasia tends to present before birth and in early infancy. Infants with hypophosphatasia are born with short limbs, craniosynostosis and soft skull bones, vitamin B6-responsive seizures, and an abnormally shaped chest which can lead to further complications. Additional complications in infancy include poor feeding and a failure to gain weight, respiratory problems, and high levels of calcium in the blood (hypercalcaemia), which can lead to recurrent vomiting and kidney problems. These complications can be life-threatening. Infants who present with hypophosphatasia in the first 6 months of life have a high mortality rate, around half of infants dying within the first year of life primarily due to respiratory failure. Hypophosphatasia that manifests later in childhood or in adults is typically less severe than hypophosphatasia manifesting in infancy. Children may have short stature with bowed legs or knock knees, enlarged wrist and ankle joints, and an abnormal skull shape causing musculoskeletal pain, fatigue, exhaustion, and decreased mobility. Adult forms of hypophosphatasia are characterised by a softening of the bones, premature loss of secondary (adult) teeth and

increased risk of fractures in the foot and thigh bones, bone pain, joint pain, decreased mobility, fatigue, exhaustion, and inflammation. Physical symptoms can severely impact quality of life.

The prevalence of severe forms of hypophosphatasia, (that is, those which present at birth or in early childhood), is unknown in England. However, in Europe, the rate of perinatal/infantile hypophosphatasia is estimated as 1 per 300,000 live births. Milder forms, in which signs and symptoms have a later onset, are more common and are estimated to be present in 1 per 6,370 of the population. It is estimated that between 1 and 7 people are diagnosed with perinatal- and infantile-onset hypophosphatasia each year in England.

Diagnosis is made on the basis of physical and radiographic findings consistent with hypophosphatasia and low or abnormal serum alkaline phosphatase. There is no standardised diagnostic algorithm. There is currently no treatment for hypophosphatasia. Medical management is aimed at monitoring and alleviating symptoms and decreasing morbidity. Vitamin B6 may also be given to reduce seizures.

This is a re-evaluation of NICE highly specialised technologies guidance on asfotase alfa for treating paediatric-onset hypophosphatasia (HST6), in line with the completion of the managed access agreement.

## The technology

Asfotase alfa (Strensiq, Alexion Pharma UK) is a recombinant fusion protein that includes the catalytic domain of human tissue non-specific alkaline phosphatase and a peptide that targets the enzyme to bone. It is a targeted enzyme replacement therapy designed to restore the regulation of metabolic processes in the bones and teeth and reduce complications of dysregulated bone mineral metabolism. It is administered by subcutaneous injection.

Asfotase alfa has a marketing authorisation in the UK under exceptional circumstances for long-term enzyme replacement therapy in people with paediatric-onset hypophosphatasia to treat the bone manifestations of the disease. The marketing authorisation states that treatment with asfotase alfa should be started by a physician experienced in the management of metabolic or bone disorders.

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| **Intervention(s)** | Asfotase alfa |
| **Population(s)** | People with paediatric-onset hypophosphatasia |
| **Comparators** | Best supportive care |
| **Outcomes** | The outcome measures to be considered include:<br>• mortality<br>• radiographic response |

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| | • severity of rickets<br>• pain<br>• respiratory function<br>• craniosynostosis and intracranial pressure<br>• growth<br>• tooth loss<br>• cognitive development and motor skills<br>• adverse effects of treatment<br>• health-related quality of life (for patients and carers). |
| **Nature of the condition** | • disease morbidity and patient clinical disability with current standard of care<br>• impact of the disease on carer's quality of life<br>• extent and nature of current treatment options |
| **Clinical Effectiveness** | • overall magnitude of health benefits to patients and, when relevant, carers<br>• heterogeneity of health benefits within the population<br>• robustness of the current evidence and the contribution the guidance might make to strengthen it<br>• treatment continuation rules (if relevant) |
| **Value for Money** | • Cost effectiveness using incremental cost per quality-adjusted life year<br>• Patient access schemes and other commercial agreements<br>• The nature and extent of the resources needed to enable the new technology to be used |
| **Impact of the technology beyond direct health benefits** | • whether there are significant benefits other than health<br>• whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services<br>• the potential for long-term benefits to the NHS of research and innovation<br>• the impact of the technology on the overall |

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| | delivery of the specialised service<br>• staffing and infrastructure requirements, including training and planning for expertise. |
| **Other considerations** | • Guidance will only be issued in accordance with the marketing authorisation.<br>• Guidance will take into account any Managed Access Arrangement for the intervention under evaluation<br>If the evidence allows the following subgroups will be considered:<br>• People with infantile-onset hypophosphatasia<br>• People with childhood-onset hypophosphatasia. |
| **Related NICE recommendations and NICE Pathways** | Related Highly Specialised Technologies Evaluations:<br>'Asfotase alfa for treating paediatric-onset hypophosphatasia' (2017). NICE Highly Specialised Technologies Guidance 6. Review date February 2023.<br>Related Guidelines:<br>'COVID-19 rapid guideline: rheumatological autoimmune, inflammatory and metabolic bone disorders' (2020; last updated 31st March 2021) NICE guideline NG167 |
| **Related National Policy** | Related NHS England policies:<br>The NHS Long Term Plan, 2019. The NHS long term plan<br>Other related policies:<br>Department of Health & Social Care (2021) The UK Rare Diseases Framework<br>Department of Health & Social Care (2019) The UK strategy for rare diseases: 2019 update to the Implementation Plan for England<br>UK Rare Disease Forum (2016) Delivering for patients with rare diseases: Implementing a strategy A report from the UK Rare Disease Forum<br>Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1, 2, and 3. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017 |