National Institute for Health and Care Excellence

Health Technology Evaluation

Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6) [ID3927]
Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Sheffield Children's NHS FT		
	Metabolic Support UK		
	Genetic Alliance UK		
	Alexion AstraZeneca Rare Disease		
Wording	Sheffield Children's NHS FT	Yes	Comment noted. No action required.

Section	Stakeholder	Comments [sic]	Action
	Metabolic Support UK	The wording is appropriate	Comment noted. No action required.
	Genetic Alliance UK		
	Alexion AstraZeneca Rare Disease	Yes	Comment noted. No action required.
Timing issues	Sheffield Children's NHS FT	Timing is urgent as the existing MAA is due to terminate this year	Comment noted. No action required. The appraisal has been scheduled into the work programme.
	Metabolic Support UK	Given the transformative impact of this technology, we consider this appraisal to be of high urgency to the NHS. People living with HPP have been receiving this treatment via a clinical trial and then via a Managed Access Agreement extending 5 years and 6 months. There is currently no longer-term certainty regarding the continuation of this treatment or a suitable or comparable alternative treatment option for people living with HPP.	Comment noted. No action required. The appraisal has been scheduled into the work programme.
	Genetic Alliance UK		
	Alexion AstraZeneca Rare Disease	The Managed Access Agreement ends on 2 February 2023 after which patients currently being treated with alfotase alfa may no longer have access to treatment	Comment noted. No action required. The appraisal has been scheduled into the work programme.

Section	Stakeholder	Comments [sic]	Action
Additional comments on the draft remit	Sheffield Children's NHS FT	No	Comment noted. No action required.
	Metabolic Support UK		
	Genetic Alliance UK		
	Alexion AstraZeneca Rare Disease		

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Sheffield Children's NHS FT	Current database suggests over 395 mutations are now identified. The description of "rickets" is not completely fulfilled as there is no expansion of the hypertrophic chondrocyte cell layer of the growth plate – a more accurate term would be "rickets-like features, including…" The statement "the most severe forms tend to occur before birth and in early infancy" - "occur" is an odd word to use – a better wording would be "the most severe forms tend to present before birth and in early infancy" Re diagnosis – serum alkaline phosphatase can be within the lower part of the normal range for some children – but the protein's function is abnormal. For those receiving asfotase alfa, genetic confirmation is required under the existing MAA, albeit not essential prior to starting treatment.	Background information updated in line with mutations number, description of features and symptoms and serum alkaline phosphatase abnormality.

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	Metabolic Support UK	We encourage the appraisal to further recognise the severity of symptoms presented in the background information. The scale of the negative impact symptoms has on a patients' life needs to be recognised and considered. Our recent insight work with the HPP community evidence that the symptoms of HPP have a severely debilitating impact on daily activities and quality of life. The background information should also consider. - Incorporating perinatal-onset symptoms. Perinatal lethal: shortened bones, skeletal malformations, absent/deficient bone formation, underdeveloped skull and ribs, underdeveloped lungs) Many babies stillborn others survive for a short period of time if untreated due to respiratory failure. Perinatal benign: rickets, skeletal malformations and varying severity. - The progressive nature of symptoms of paediatric-onset HPP. Infants with HPP may appear normal at birth but go on to develop progressive skeletal demineralisation. - The musculoskeletal pain experienced by paediatric patients. - Respiratory problems is a broad term. - The fatigue and exhaustion experienced by adult patients with paediatric onset HPP. - Decreased mobility in adult patients with paediatric onset HPP requires the use of walking aids and wheelchair. - Loss of bone mass and subsequent weakening of the bones, meaning they become brittle, fragile, and fracture easily. - Adult patients should include bone pain, pain is not exclusive to joint pain. In addition to the physical symptoms listed, we would like to see the inclusion of the psychosocial impact the condition has on patients and their caregivers.	Comments noted. Background information updated to include specific physical symptoms and impact to patient quality of life.

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		The mental health of those living with the condition and their caregivers should also be taken into consideration during this consultation.	
	Genetic Alliance UK	Following conversations with one of our member organisations, Metabolic Support UK, we believe that the background doesn't accurately reflect the severity of this condition for those who live with hypophosphatasia. Hypophosphatasia that onsets later in childhood or adulthood are considered less severe as they may not be fatal however these forms are still very severe and debilitating. In October 2021, Genetic Alliance UK compiled a patient perspective statement on adult hypophosphatasia for the purpose of licensing this condition for preimplantation genetic testing (PGT-M). We carried out a survey to collect the views of people living with the condition and their families or carers. During this process, individuals highlighted the burden of recurrent fractures meaning that they are not able to take part in physical activities. 'I have had multiple fractures not caused by trauma eg ribs broken by turning over in bed, feet broken by stepping off a kerb. Both femurs fractured and needed to be pinned without any trauma. This has significantly affected my mobility and causes ongoing pain.' – response from survey Individuals also experience chronic bone pain that can be worsened by putting weight through the bones. This pain impacts a person's ability to sleep.	Comments noted. Description of disease symptoms updated in line with comments. Patient perspectives and experiences will be covered in the appraisal process not at scoping.

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		Chronic bone pain and joint inflammation lead to mobility issues, this is not reflected in the draft scope. 'I am very stiff all the time and have pain when moving. There is constant gnawing bone pain which shifts throughout my body. Repetitive movements with my arms are impossible making tasks such as chopping, cutting, etc., nigh on impossible. When immobile even for short periods I feel as if I am seizing up and have difficulty moving.' – response to survey 'I have struggled with chronic joint pain for many years, I can often be completely incapacitated and need weeks off work to rest. I feel less able to care for my child and do basic daily chores.' – Response to survey	
	Alexion AstraZeneca Rare Disease	For accuracy, suggest replacing: *"Over 275 different mutations of this gene leading to hypophosphatasia have been identified"* With the following: *"Approximately 500 mutations of this gene leading to hypophosphatasia have been identified to date"* (Reference: The ALPL gene homepage - Global Variome shared LOVD. [online] Databas-es.lovd.nl. Available at: https://databases.lovd.nl/shared/genes/ALPL (Accessed: April 2022)) For completeness, after the sentence: *"This leads to rickets, softening and weakening of the bones (osteomalacia), bone deformity and a greater incidence of fractures."* Suggest adding: *"Fractures are particularly common in adults but less common in children"*	Comments noted. Background information updated in line with: • Mutations number updated in line with figures provided by Alexion AstraZeneca Rare Disease and Sheffield Children's NHS FT • Differentiation of fracture prevalence • Description of disease

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		(Reference: Alexion. Fifth progress report ALX-HPP-501 an Observational, Longitudinal, Prospective, Long-Term Registry Of Patients With Hypophosphatasia. 19 August 2021. Data on file) For completeness, after the sentence: *"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)."* Suggest adding: *"This is a historical classification that is currently being questioned because of a significant overlap in symptomatology regardless of onset. There is a clear distinction between perinatal/infantile hypophosphatasia that is usually lethal and patients who manifest the disease after the first 6 months of life, but beyond that these separations are artificial."* (Reference: This is described by Dr. Whyte; Michael P. Whyte, Chapter 22 - Hypophosphatasia,Editor(s): Rajesh V. Thakker, Michael P. Whyte, John A. Eisman, Takashi Igarashi,Genetics of Bone Biology and Skeletal Disease, Academic Press, 2013, Pages 337-360, ISBN 9780123878298, https://doi.org/10.1016/B978-0-12-387829-8.00022-6. (https://www.sciencedirect.com/science/article/pii/B9780123878298000226)) For accuracy, suggest replacing: *"The most severe forms of the condition tend to occur before birth and in early infancy."* With the following: *"The most severe hypophosphatasia tends to occur before birth and in early infancy."*	manifestation, symptoms and severity Prevalence and severity of symptoms within broad terms will be discussed during the appraisal process.

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		For completeness, suggest replacing: *"Infants with hypophosphatasia are born with short limbs, an abnormally shaped chest, and soft skull bones."* With the following: *"Infants with hypophosphatasia are typically born with short limbs, an abnormally shaped chest with hypomineralized and gracile ribs that may lead to the inability of the rib cage to support normal respiratory function and increase the risk of ventilator dependence and premature death, soft skull bones, craniosynostosis, and vitamin B6-responsive seizures"* (Reference: Högler W, et al. BMC Musculoskelet Diord. 2019;20(1):80) For accuracy, suggest replacing: *"The forms of hypophosphatasia that appear later in childhood or in adults are typically less severe than those that appear in infancy."* With the following: *"Hypophosphatasia that manifests later in childhood or in adults is typically less severe than hypophosphatasia manifesting in infancy."* For accuracy and completeness, suggest replacing: *"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, joint pain and inflammation."* With the following: *"Hypophosphatasia in adults is characterised by a softening of the bones, dental abnormalities and premature loss of secondary (adult) teeth, abnormal gait,*	

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		muscle weakness, an increased risk of fractures in the foot and thigh bones, recurrent and pseudofractures and joint pain and inflammation." (References: Hogler W, et al. BMC Musculoskelet Disord. 2019;20:80; Conti F, et al. Clin Cases Miner Bone Metab. 2017;14(2):230–234; Seefried L, et al. J Bone Miner Res. 2020;35(11):2171–2178;) For accuracy, suggest replacing: *"The prevalence of severe forms of hypophosphatasia, (that is, those which present at birth or in early childhood), is unknown in England."* With the following: *"The true prevalence of hypophosphatasia is unknown in England."* For accuracy, suggest replacing: *"However, in Europe, the rate is estimated as 1 per 300,000 live births"* With the following: *"However, in Europe, the rate of perinatal/infantile hypophosphatasia is estimated as 1 per 300,000 live births."* (Reference: Mornet E, Yvard A, Taillandier A, Fauvert D, Simon-Bouy B. A molecular-based estimation of the prevalence of hypophosphatasia in the European population. Ann Hum Genet. 2011;75(3):439–45.) For accuracy, suggest replacing: *"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."* With the following:	

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		"Heterozygosity is more common and is estimated to be present in 29 per 100,000 adults." (Reference: Tornero C, Navarro-Compán V, Tenorio JA, García-Carazo S, Buño A, Monjo I, Plasencia-Rodriguez C, Iturzaeta JM, Lapunzina P, Heath KE, Balsa A. Can we identify individuals with an ALPL variant in adults with persistent hypophosphatasaemia?. Orphanet journal of rare diseases. 2020 Dec;15(1):1-9.) For completeness, after the sentence: *"Diagnosis is made on the basis of physical and radiographic findings consistent with hypophosphatasia and low serum alkaline phosphatase."* Suggest adding: *"ALPL genetic testing and elevated substrates, such as PLP and/or PEA, may support the diagnosis"* (Reference: Kishnani PS. Mol Genet Metab. 2017;122(1-2):4–17; 2.) For accuracy, suggesting replacing: *"There is currently no treatment for hypophosphatasia."* With the following: *"Asfotase alfa has a marketing authorisation in the UK 'for long-term enzyme replacement therapy in patients with paediatric-onset hypophosphatasia to treat the bone manifestations of the disease'. It is used for routine clinical practice under a managed access agreement (HST6) criteria"* (Asfotase Alfa SmPCs are available: https://www.medicines.org.uk/emc/search?q=strensiq)	
Population	Sheffield Children's NHS FT	Correctly defined	Comment noted. No action required.

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	Metabolic Support UK	We do not have evidence to suggest that the population has or has not been defined appropriately. We support the routing of this appraisal, given the small patient population in England. We also support the consideration of the proposed sub-groups outlined in the draft scope; People with infantile-onset hypophosphatasia, People with childhood-onset hypophosphatasia, should the evidence allow.	Comment noted. No action required.
	Genetic Alliance UK		
	Alexion AstraZeneca Rare Disease	No comments	Comment noted. No action required.
Subgroups	Sheffield Children's NHS FT	No other subgroups	Comment noted. No action required.
	Metabolic Support UK		
	Genetic Alliance UK		
	Alexion AstraZeneca Rare Disease	No comments	Comment noted. No action required.

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Comparators	Sheffield Children's NHS FT	Comparators are correct at present.	Comment noted. No action required.
	Metabolic Support UK	We feel it is inappropriate to use best supportive care as a comparator during this consultation. There is currently no diagnostic, care or treatment pathway to which the technology can be compared. There are currently no best practices, standards, or guidelines on how to treat HPP or best supportive care models within the wider rare landscape. We recommend this comparator is removed from the consultation.	Comment noted. No action taken.
	Genetic Alliance UK		
	Alexion AstraZeneca Rare Disease	No comments	Comment noted. No action required.
Outcomes	Sheffield Children's NHS FT	If motor skills includes later motor function (including six minute walk test, brief assessment of motor function) then yes; it would be appropriate, perhaps, to separate motor skills and cognitive development – whilst they are intimately linked in early life, that is not true later. Could also include fractures as an outcome – both their occurrence and the time taken to heal or the persistence of non-union As use of aids to mobility is one of the MAA start criteria for children, this should be included Joint disease – osteoarthropathy, chondrocalcinosis, periarticular calcifications need to be considered in adult patients It is not clear to me that craniosynostosis is an outcome measure that is affected by the intervention – it is part of the underlying disease	Comments noted. No action taken. Specific outcome measures within broad terms are expected to be discussed during the appraisal process.

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	Metabolic Support UK	The background information does not include fatigue or mobility as a symptom of this condition and our engagement with people living with HPP indicates these are key symptoms impacting patient quality of life. As such, fatigue and mobility should be an outcome measure when evaluating the benefits of this technology. A reduction on the reliance of other treatments such as pain medication, should also be considered as an outcome measurement. The psycho-social aspects within the health-related quality of life (for patients and carers) should be explicitly reviewed, such as significant strains on the family unit, employment, education, support network and relationships. Given the negative impacts of the condition highlighted in the background information, mental health would be an appropriate outcome measure when evaluating the benefits of this technology. Lastly, 'adverse effects of treatment' has been included as an outcome measure. We would encourage that this outcome measure takes consideration to the disruptions and burden caused by conventional symptomatic treatment options and the potential for the technology to alleviate these.	Comments noted. No action taken. Specific outcome measures within broad terms are expected to be discussed during the appraisal process.
	Genetic Alliance UK	As mentioned above, mobility has not been considered in the draft scope. We have been informed by Metabolic Support UK that a 6 minute walk test is often a criteria for treatment and therefore mobility should be included in the outcomes.	Comments noted. No action taken. Specific outcome measures within broad terms are expected to be discussed during the appraisal process.
	Alexion AstraZeneca Rare Disease	No comments	Comment noted. No action required.

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Equality	Sheffield Children's NHS FT	Equality requirements seem to be met	Comment noted. No action required.
	Metabolic Support UK	The current eligibility criteria under the managed access scheme, excludes some HPP (paediatric-onset) patients from accessing this technology, impacting equity and access to this technology. It is not clear whether these criteria will be applied should the technology receive a positive recommendation, therefore we seek further clarity from NICE in this regard.	
	Genetic Alliance UK		
	Alexion AstraZeneca Rare Disease	No comments	Comment noted. No action required.
Other considerations	Sheffield Children's NHS FT		
	Metabolic Support UK	The impact of HPP exceeds the health-related aspects of a patient's life and consideration should be given to the psychosocial aspects outlined below. - Mental and emotional health - Ability to carry out daily activities - Social interactions/integration into society.	Comment noted. No action taken. Health-related quality of life measures should intrinsically capture impacts to aspects listed. Financial burden to patients and carers is not

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		- Education - Employment - Family cohesion - Wider support networks - The ability to travel The impact on parent/caregivers should also be considered during the evaluation of this technology. Finally, the financial burden of HPP is also significant and should be considered during the evaluation.	considered in the NICE reference case.
	Genetic Alliance UK		
	Alexion AstraZeneca Rare Disease	No comments	Comment noted. No action required.
Innovation	Sheffield Children's NHS FT	The technology has been employed under an MAA for the last 5 years – the impact should be assessed in the light of the real world evidence collected as part of the MAA. However, such data cannot answer the "what if it had not been used" question without extrapolation from the known information on natural history of the condition. In comparing the cost of the intervention (asfotase alfa) with "standard of care" does the comparison assume that the patient with severe infantile-onset disease would have been ventilated, as part of "standard of care", to support their deteriorating respiratory function, and therefore look at the costs of long term ventilatory support and any other costs that might arise in such a situation?	

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	Metabolic Support UK	We consider this to be a step-change technology. We recommend that the psychosocial impact of HPP is considered in addition to or included in the QALY calculation.	
	Genetic Alliance UK		
	Alexion AstraZeneca Rare Disease	Asfotase alfa is the only treatment that has a marketing authorisation in the UK for long-term enzyme replacement therapy in patients with paediatric-onset hypophosphatasia to treat the bone manifestations of the disease	
Questions for consultation	Sheffield Children's NHS FT	Do the comparators include the use of long-term ventilatory support for affected untreated individuals? For those not receiving asfotase alfa, treatment is symptomatic and supportive, and may include analgesics, occupational and physiotherapy inputs to address mobility issues resulting from muscle weakness and ligamentous laxity, and surgical management of craniosynostosis and fixation of non-healing fractures	
	Metabolic Support UK		
	Genetic Alliance UK		
	Alexion AstraZeneca Rare Disease	**Question:** Have all relevant comparators for asfotase alfa been included in the scope? **Response:** There are no licensed comparators available, only supportive care **Question:** Which treatments are considered to be established clinical practice in the NHS for treating paediatric-onset hypophosphatasia?	

Section	Consultee/ Commentator	Comments [sic]	Action
		Response: Asfotase alfa under managed access agreement (HST6) **Question:** How should best supportive care be defined? **Response:** Treatments directed toward specific symptoms and complications. **Question:** Are the outcomes listed appropriate? **Response:** Yes **Question:** Are the proposed subgroups appropriate? Are there any other subgroups of people in whom asfotase alfa is expected to provide greater clinical benefits or more value for money, or that should be examined separately? **Response**: Proposed subgroups appropriate	
Additional comments on the draft scope	Sheffield Children's NHS FT	Are the current MAA criteria appropriate for starting/stopping treatment? Should a national authorisation panel continue to operate as it does currently to review all the treated individuals, and how should the membership of the panel be determined and refreshed? Should data collection at the level/intensity of the MAA be continued for treated individuals? How is the funding to support that detailed data collection within the NHS identified and made available to those actually undertaking the work?	
	Metabolic Support UK		
	Genetic Alliance UK		

Section	Consultee/ Commentator	Comments [sic]	Action
	Alexion AstraZeneca Rare Disease	No further comments	Comment noted. No action required.