NICE National Institute for Health and Care Excellence

NICE guidance

Asfotase alfa for treating paediatric-onset hypophosphatasia

Highly specialised technologies guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces HST6.

1 Recommendations

1.1 Asfotase alfa is recommended as an option for treating paediatric-onset hypophosphatasia if the person's symptoms started before or at birth (perinatal onset) or between the ages of 0 and 6 months (infantile onset). It is also recommended for people whose symptoms started between the ages of 6 months and 17 years (juvenile onset) only if:

- they are aged 1 year to 4 years and have:
  - not reached expected developmental gross motor milestones for their age or
  - continuing or recurring significant musculoskeletal pain that affects daily activities and quality of life, and has not improved after 2 different types of painkiller recommended by a national pain specialist
- they are aged 5 years to 18 years and have:
  - limited mobility assessed by a specialist using the modified Bleck Ambulation Efficiency Score and a Bleck score between 1 and 6 or
  - continuing or recurring significant musculoskeletal pain that affects daily activities and quality of life, and has not improved after 2 different types of painkiller recommended by a national pain specialist
- they are over 18 years and have 2 or more of the following:
  - current fractures with a history of non-traumatic, recurring or non- or poorly healing fractures
  - limited mobility assessed by a specialist using the modified Bleck Ambulation Efficiency Score and a Bleck score between 1 and 6
  - continuing or recurring significant musculoskeletal pain that affects daily activities and quality of life, and has not improved after 2 different types

of painkiller recommended by a national pain specialist.

Asfotase alfa is only recommended if the company provides it according to the commercial arrangement.

Why the committee made this recommendation

This evaluation reviews the evidence for asfotase alfa for treating paediatric-onset hypophosphatasia (NICE highly specialised technologies guidance 6), including evidence collected as part of the managed access agreement.

Paediatric-onset hypophosphatasia is a rare genetic condition that affects how calcium and phosphorous are deposited in developing bones and teeth. It includes perinatal-, infantile- and juvenile-onset forms of the disease. There are limited treatment options and it can substantially affect the lives of people with the condition and their families and carers. People with perinatal- or infantile-onset hypophosphatasia can have breathing complications, craniosynostosis (when the bones in a baby's skull join together too early) and pressure around the brain. The risk of death in the first year of life in these populations is high. The risk of death is lower for people with juvenile-onset hypophosphatasia. But, juvenile-onset hypophosphatasia can be associated with severe symptoms that affect quality of life, including impaired mobility, pain and regular fractures. Because of the difference in severity, the committee considered the 2 populations separately.

In perinatal- or infantile-onset hypophosphatasia, asfotase alfa is likely to increase how long people live before needing a ventilator and how long people live overall compared with best supportive care. In juvenile-onset hypophosphatasia, asfotase alfa is likely to improve outcomes including mobility, pain and health-related quality of life compared with best supportive care.

In perinatal- and infantile-onset populations, the cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So asfotase alfa is recommended for all people in these groups.

In juvenile-onset populations, the cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources when symptoms are more severe. So asfotase alfa is only recommended for juvenile-onset hypophosphatasia with severe symptoms.

2 Information about asfotase alfa

Marketing authorisation indication

2.1 Asfotase alfa (Strensiq, Alexion Pharma UK) is indicated for 'long-term enzyme replacement therapy in patients with paediatric-onset hypophosphatasia to treat the bone manifestations of the disease'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for asfotase alfa.

Price

2.3 The list prices for asfotase alfa are:

- £12,700.80 per 12-injection vial, which contains 18 mg/0.45 ml of asfotase alfa (excluding VAT; BNF online, accessed December 2022)
- £19,756.80 per 12-injection vial, which contains 28 mg/0.7 ml of asfotase alfa (excluding VAT; BNF online, accessed December 2022)
- £28,224.00 per 12-injection vial, which contains 40 mg/1 ml of asfotase alfa (excluding VAT; BNF online, accessed December 2022)
- £56,448.00 per 12-injection vial, which contains 80 mg/0.8 ml of asfotase alfa (excluding VAT; BNF online, accessed December 2022).

  The company has a commercial arrangement. This makes asfotase alfa available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The evaluation committee considered evidence submitted by Alexion Pharma UK, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Paediatric-onset hypophosphatasia

3.1 Hypophosphatasia is a genetic disorder caused by mutations in the ALPL gene, which leads to a deficiency in tissue non-specific alkaline phosphatase (TNSALP) enzyme activity. This causes disruption of mineralisation, a process in which calcium and phosphorous are deposited in developing bones and teeth. Several clinical forms of hypophosphatasia are currently recognised:

- perinatal onset (symptoms starting before or at birth)
- infantile onset (symptoms starting at 0 to 6 months)
- juvenile onset (also referred to as childhood onset; symptoms starting between 6 months and 17 years)
- adult onset (symptoms starting at 18 years and over) and
- odontohypophosphatasia (only dental symptoms).

Paediatric-onset hypophosphatasia includes everyone with hypophosphatasia of perinatal, infantile or juvenile onset. Adult-onset hypophosphatasia and odontohypophosphatasia are outside the scope of this guidance. The signs and symptoms of hypophosphatasia vary widely and can appear any time from before birth to adulthood. They include rickets, softening and weakening of the bones (osteomalacia), bone deformity and a greater incidence of fractures. Hypophosphatasia can also lead to chronic debilitating pain, muscle weakness, generalised seizures because of vitamin B6 deficiency, and renal and respiratory complications. The most severe

forms of the condition tend to occur before birth and in early infancy. Babies who present with hypophosphatasia in the first 6 months of life (that is, babies with perinatal- or infantile-onset disease) have a high mortality rate. About 50% to 100% of babies die within the first year of life, primarily because of respiratory failure. Juvenile-onset hypophosphatasia, which develops later in childhood, has a substantially lower mortality rate. But, it is often debilitating and leads to bone deformities that may result in delayed walking, limb weaknesses, skeletal pain and non-traumatic fractures. The clinical experts explained that the severity of symptoms in this group vary between individuals and may progress over time. The committee concluded that the age that symptoms start influences the mortality associated with perinatal- or infantile-onset hypophosphatasia, and can also correlate to the morbidity associated with hypophosphatasia, although morbidity can vary from person to person.

Effects on quality of life

3.2 Patient experts and patient groups described how hypophosphatasia is a debilitating condition in all age ranges and that it impacts people physically, socially and emotionally. For people with perinatal- or infantile-onset hypophosphatasia, respiratory compromise and seizures have the greatest effect on health-related quality of life. Babies who survive have significant ongoing morbidity and may still need invasive ventilation, further impairing their health-related quality of life. Hypophosphatasia in babies can also lead to difficulties with crawling, growth and feeding, which impacts the whole family. Poor mobility makes everyday activities and independent living difficult for adults and children, with walking aids or home adaptations needed. People who have hypophosphatasia find working very challenging because of physical limitations, mental challenges, sickness and time needed off work to attend appointments. Hypophosphatasia makes it difficult to have a normal and enjoyable social life and education can also be affected. There is also a large burden on carers of people who have hypophosphatasia, particularly carers of babies. Carers are likely to spend many days in hospital with their child, which reduces time with other family members and results in time away from work (or stopping work entirely). It is difficult to manage childcare and hospital appointments, which also often involve extra travel burden. Because of the rarity of hypophosphatasia there is little

information or advice available. Families must adapt their hobbies and social lives around their child's hypophosphatasia, and parents can experience long-term mental health problems. The daily lives of carers of children with perinatal- or infantile-onset hypophosphatasia are affected because of the child's seizures and the need to regularly monitor oxygen levels. Patient experts highlighted that because of the limited numbers of centres treating hypophosphatasia in England, long journeys for appointments or inpatient stays may be needed regularly. The committee concluded that hypophosphatasia has a substantial impact on people with the condition and their families and carers.

Clinical management

Managed access agreement and starting criteria

3.3 Asfotase alfa has been available through a managed access agreement (MAA) since the original NICE highly specialised technologies guidance for asfotase alfa (from here referred to as HST6) was published in 2017. The MAA required collection of data on people having treatment and their families. Before this, the only treatment option was best supportive care. Best supportive care varies according to the type and severity of symptoms, but includes surgical, therapeutic and dental management techniques. The MAA had starting criteria specifying that only people with symptoms associated with severe hypophosphatasia should be treated with asfotase alfa. This included all people with perinatal- or infantile-onset hypophosphatasia. It also included people with severe symptoms of juvenile-onset hypophosphatasia, including:

- children aged 1 year to 4 years who have:
  - not reached expected developmental gross motor milestones for their age or
  - continuing or recurring significant musculoskeletal pain that affects daily activities and quality of life, and has not improved after 2 different types of painkiller recommended by a national pain specialist
- children and young people aged 5 years to 18 years who have:

  - limited mobility assessed by a specialist using the modified Bleck Ambulation Efficiency Score and a Bleck score between 1 and 6 or
  - continuing or recurring significant musculoskeletal pain that affects daily activities and quality of life, and has not improved after 2 different types of painkiller recommended by a national pain specialist

- adults over 18 years who meet 2 or more of the following criteria have:
  - limited mobility assessed by a specialist using the modified Bleck Ambulation Efficiency Score and a Bleck score between 1 and 6 or
  - continuing or recurring significant musculoskeletal pain that affects daily activities and quality of life, and has not improved after 2 different types of painkiller recommended by a national pain specialist
  - current fractures with a history of non-traumatic, recurring or non- or poorly healing fractures.

Treatment aims

3.4 The main goal of treatment in those most severely affected by hypophosphatasia, which is life threatening, is to keep them alive. For people have less-severe disease, treatment goals include:

- improving bone mineralisation
- minimising risk of seizures and respiratory complications in babies and children
- attaining growth and developmental milestones in children
- reducing the number and frequency of fractures
- reducing pain
- improving ambulation
- improving oral health

- improving quality of life for the person with hypophosphatasia and their carer.

  Patient groups said that asfotase alfa has been life saving for babies and life changing for all people, with a clear impact on overall health for people with hypophosphatasia and their families and carers. Benefits include:

- the need for fewer medical appointments
- improved mobility
- children being able to breathe independently
- better control of symptoms
- improved performance in school
- improved work and social life
- improved quality of life.

  These benefits were said to outweigh difficulties with administration of asfotase alfa in babies and young children. Clinical experts described how asfotase alfa has had a big impact on both morbidity and mortality whilst reducing the reliance on carers.

Clinical effectiveness

Data sources

3.5 Evidence on asfotase alfa for this review came from 6 sources. This included 4 clinical trials that were considered by the committee in the original appraisal and new data from 2 real-world studies. The clinical trials were phase 2 open-label studies of asfotase alfa (2 of which had associated extension studies):

- ENB-002-08 was a non-randomised 24-week single-arm study in 11 people of 36 months and under with infantile-onset hypophosphatasia, with an extension study (ENB-003-08) that followed 10 people for up to 7 years.

- ENB-010-10 was a non-randomised, dose-comparison study of asfotase alfa treatment in 69 people of 5 years and under, with perinatal- or infantile-onset hypophosphatasia followed for up to 6 years.
- ENB-006-09 was a randomised 24-week dose-comparison study in 13 people of 5 years to 12 years with paediatric-onset hypophosphatasia, with an extension study ENB-008-10 that followed 12 people for up to 7 years.
- ENB-009-10 was a randomised, 24-week concurrent control study in 19 people of 13 years to 65 years, with hypophosphatasia (18 of 19 people had paediatric-onset hypophosphatasia) followed for up to 5 years.

  Real-world data was collected under the managed access agreement (UK MAA data) in people with paediatric-onset hypophosphatasia, regardless of current age, who had asfotase alfa. Follow up was up to 4 years. Further real-world data is available from the ongoing Global Hypophosphatasia Registry and includes people who have had asfotase alfa and people who have not. The outcomes included in the trials and real-world studies were similar and included:

- mortality
- pain
- mobility
- radiographic response
- severity of rickets
- respiratory function
- craniosynostosis and intracranial pressure
- growth
- tooth loss
- cognitive development and motor skills

- adverse effects of treatment
- fractures
- health-related quality of life.

The company's comparative analysis that it included in its submission focused on overall survival and ventilator-free survival (see section 3.8). In response to the draft guidance consultation, the company presented further comparative evidence specific to the juvenile-onset population. This focused on outcomes including mobility, pain, growth and health-related quality of life. The committee considered all sources of evidence within its decision making.

Categorisation of population

3.6 In the UK MAA data presented by the company, results were presented by age at study entry: under 18 years or 18 years and over. For the ENB-009-10 study (n=19), results were presented for the whole trial population, which included 18 people with paediatric-onset hypophosphatasia. The EAG noted that these categories did not align with the accepted categories of paediatric-onset hypophosphatasia: perinatal, infantile and juvenile onset. This made it difficult to assess the data against the decision problem and between asfotase alfa trials. The company highlighted that the MAA from HST6 did not require data to be collected by age at onset of symptoms. It also reported that ENB-006-08/ ENB-008-10 included subgroup analysis for juvenile-onset hypophosphatasia when the results were similar to the main analysis. The EAG said that all relevant evidence should have been included and categorised as per the subgroups in the scope for the whole paediatric-onset population. The experts described how there is a lot of overlap in people with perinatal- and infantile-onset hypophosphatasia, but that people with juvenile-onset hypophosphatasia have a different prognosis. Bone issues are common across all forms of paediatric-onset hypophosphatasia. But mortality is much higher in people with perinatal- or infantile-onset hypophosphatasia, especially in the first year of life. The clinical experts explained that although the symptoms of hypophosphatasia are highly debilitating, they are not in themselves necessarily life threatening. But symptoms

such as limited mobility are likely to contribute to increased risk of comorbidities, such as cardiovascular disease, which would lead to increased mortality. The clinical experts also explained that there is a subgroup of people with juvenile-onset hypophosphatasia who have more severe disease and these people are identifiable in clinical practice. They explained that treatment of juvenile-onset hypophosphatasia with asfotase alfa is only allowed once physiotherapy and analgesics have failed to provide sufficient benefit. The decision to use asfotase alfa is made by the National Severity Panel. Therefore, only severe juvenile-onset hypophosphatasia is treated with asfotase alfa. The clinical experts explained that the starting rules for asfotase alfa included in the original MAA were broadly appropriate for identifying people with the most severe symptoms of juvenile-onset hypophosphatasia. People with perinatal- or infantile-onset hypophosphatasia who survive will likely experience greater challenges throughout childhood and have different complications than people with juvenile-onset hypophosphatasia because of the severity of illness they experienced as babies. The committee concluded that evidence should be presented for perinatal- or infantile-onset hypophosphatasia and juvenile-onset hypophosphatasia separately because prognosis varies between these 2 groups. It also concluded that there was an identifiable subgroup of people with juvenile-onset hypophosphatasia with severe disease, in line with the starting rules for asfotase alfa in the original MAA from HST6.

Population in the decision problem and clinical efficacy evidence provided

3.7 In its submission, the company's analyses comparing asfotase alfa with best supportive care were in people with perinatal- or infantile-onset hypophosphatasia. The comparative analyses initially done by the company (see section 3.8) did not include people with juvenile-onset hypophosphatasia. The EAG highlighted that this meant there was a lack of evidence about the relative efficacy of asfotase alfa in relation to best supportive care in this subgroup. The company stated that a pooled analysis for this group was inappropriate for several reasons. These included that:

- current clinical status is more important than age at onset
- the majority of the clinical trials were based around age at enrolment rather

than onset

- there is substantial variation in study inclusion criteria, making pooling difficult, and that survival analysis are not relevant in this group because hypophosphatasia is not typically life threatening.

The EAG acknowledged that there are limitations with all sources of comparative data. But, the EAG did not consider that the comparative efficacy of asfotase alfa and best supportive care were suitably addressed for all populations and outcomes in the scope from the data available. The experts explained that the prognosis of people with perinatal- or infantile-onset hypophosphatasia is different to people with juvenile-onset hypophosphatasia (see section 3.6). In response to the draft guidance consultation, the company presented naive comparative evidence of asfotase alfa and best supportive care for people with juvenile-onset hypophosphatasia from ENB-006-09/ENB-008-10, ENB-009-10, the UK MAA and the Global Hypophosphatasia Registry (see section 3.5). The company explained that methods for adjusting for potential confounders in comparative analyses were not feasible because of differences in disease severity within each data source. The EAG agreed that it was not feasible to match the data in comparative analyses. The committee concluded that analyses comparing asfotase alfa with best supportive care presented by the company in both the perinatal- or infantile-onset and the juvenile-onset subgroups are sufficient for decision making.

Comparative analysis for perinatal- or infantile-onset hypophosphatasia

3.8 The company did a comparative analysis of overall survival and ventilator-free survival in people with perinatal- or infantile-onset hypophosphatasia only. Data on people who had had asfotase alfa was taken from ENB-002-08/ENB-003-08 (n=11) and ENB-010-10 (n=69). Data on best supportive care was taken from untreated historical controls from ENB-011-10, a global non-interventional, retrospective, epidemiologic chart review study including 48 people. The comparative analysis showed that asfotase alfa significantly improved overall survival at 7 years (87% survival; 95% confidence interval [CI] 0.77 to 0.93)

compared with best supportive care (27% survival; 95% CI 0.15 to 0.40). Ventilator-free survival at 7 years was also significantly improved (81% [95% CI 0.68 to 0.89] compared with 25% [95% CI 0.14 to 0.38]). The EAG considered that this comparative analysis is a form of indirect treatment comparison, but that the methods were flawed (see section 3.9, section 3.10 and section 4.11). It also stated that comparative analyses should be conducted for all relevant outcomes using all relevant data for people having asfotase alfa and for those having best supportive care. Despite limited data, this should not stop a comparison being made. The clinical experts explained that since asfotase alfa has been available, there have been improvements in mortality and morbidity. They added that people with perinatal- or infantile-onset hypophosphatasia who would not have survived previously now do. This makes quantifying the benefit on morbidity difficult. The committee concluded that survival outcomes in people with perinatal- or infantile-onset hypophosphatasia are improved with asfotase alfa but recognised the uncertainty in the analyses described in sections 3.9, 3.10 and 3.11. It further recognised that some benefit is expected in other outcomes.

Changes in best supportive care

3.9 The company used historical control data in its comparative analysis (see section 3.8) to inform the effectiveness of best supportive care. The EAG was concerned that the data used was mostly from people who were diagnosed with hypophosphatasia and started treatment before the year 2000. At that time, people having best supportive care did not live for as long as they do today. The EAG said that this may bias the results of the comparative analysis in favour of asfotase alfa. The experts said that there may have been improvements in respiratory care in the last 20 years. However, best supportive care has not changed otherwise and would not alter long-term survival, because bone mineralisation is not affected by respiratory care. The EAG suggested that the company should have used all available data on best supportive care to inform the comparison, including data from the Global Hypophosphatasia Registry. The company stated that the Global Hypophosphatasia Registry has only existed since asfotase alfa has been available. Therefore, the people in the registry with hypophosphatasia who are having best supportive care, have less-severe disease than those having asfotase alfa. The clinical experts agreed that people who had asfotase alfa as part of the MAA from HST6 are unlikely to be

comparable with people having best supportive care in the Global Hypophosphatasia Registry. The company also said that the number of people with perinatal- or infantile-onset hypophosphatasia in the Global Hypophosphatasia Registry is small, with only 1 person having died. The committee concluded that the use of the historical data may bias the results of the comparative analysis in favour of asfotase alfa. But, if the Global Hypophosphatasia Registry data had been sufficient for use, this may have biased the results in favour of best supportive care.

Potential for immortal time bias in the overall survival comparison

3.10 The company used historical control data in its comparative analysis for the perinatal- or infantile-onset subgroups (see section 3.8) to inform the effectiveness of best supportive care. The EAG was concerned about the potential for immortal time bias within the comparison, which would bias the results in favour of asfotase alfa. The Kaplan–Meier curves based on 'survival from birth' can erroneously indicate that people having asfotase alfa had it from birth, whereas they were given treatment only after the study enrolment. Immortal time bias can occur, in observational studies, when there is a delay in starting treatment. This wait period is considered immortal because individuals who enter the treatment group have survived until treatment is started. The death of more severely affected people can occur between birth and treatment initiation. In ENB-002-08/ENB-003-08 children with hypophosphatasia aged 3 years or below were enrolled, meaning that people who had survived infancy were included and had asfotase alfa. In the natural history study (ENB-011-10) used for the comparison, this bias could not occur because people were likely followed from a younger age. The company excluded people who had best supportive care and died on the first day after baseline, because these people would be unlikely to start on asfotase alfa treatment to help reduce the potential for bias. The committee concluded that there is the potential for immortal time bias to occur in the comparative analysis and that it would ideally prefer the survival analysis to censor matched people having best supportive care until they would otherwise have had the opportunity to have asfotase alfa. The committee recognised that limitations with the availability of data may have prevented this type of analysis being done.

Long-term analysis for juvenile-onset hypophosphatasia

3.11 In response to the draft guidance consultation, the company presented long-term follow-up data for asfotase alfa in the juvenile-onset population from single-arm clinical trials (ENB-006-09/ENB-008-10 and ENB-009-10), the UK MAA and the Global Hypophosphatasia Registry. The data reported across outcomes is academic in confidence and cannot be reported here. All 3 sources indicated that asfotase alfa was associated with an improvement from baseline in mobility on the 6-minute walk test (6MWT) and in patient-reported pain on the Brief Pain Inventory Short Form (BPI-SF) severity scale. Data from the UK MAA and the Global Hypophosphatasia Registry also indicated that asfotase alfa was associated with an improvement from baseline in health-related quality of life. The EAG highlighted that the company reported inconsistent baseline data and therefore it was unclear if all the available data has been included in all the analyses. It also noted that the number of participants with data reported in the UK MAA and the Global Hypophosphatasia Registry were very low and it was unclear if this was because of loss to follow up or immature follow up. The committee concluded that the small amount of evidence presented suggested that asfotase alfa was effective in the juvenile-onset population for the outcomes reported, although the data is uncertain.

Comparative analysis for juvenile-onset hypophosphatasia

3.12 In response to the draft guidance consultation, the company presented comparative evidence of asfotase alfa and best supportive care for people with juvenile-onset hypophosphatasia from ENB-006-09/ENB-008-10 and ENB-009-10. This data is academic in confidence and cannot be reported here. Results from ENB-006-09/ENB-008-10 indicated that asfotase alfa improved rickets severity measured on the Radiographic Global Impression of Change compared with untreated historical controls (see section 3.9). ENB-009-10 included a 6-month primary treatment period with a control group given best supportive care. Results from this 6-month primary treatment period indicated that asfotase alfa improved mobility on the 6MWT and gross motor function on the Bruininks-Oseretsky Test Running Speed and Agility score compared with best supportive care controls. Changes from baseline in patient-reported pain on the BPI-SF were similar between people treated with asfotase alfa and best

supportive care at 6 months follow up. The company also presented naive comparative evidence of people with hypophosphatasia treated with asfotase alfa from the ENB-006-09/ENB-008-10, ENB-009-10, the UK MAA data and the Global Hypophosphatasia Registry, compared with people whose disease had not been treated with asfotase alfa in the Global Hypophosphatasia Registry. The company highlighted that there are major differences in the baseline data between these sources and between people in the Global Hypophosphatasia Registry who have had asfotase alfa and whose disease has never been treated with asfotase alfa. This is because people in the registry who are having best supportive care have less-severe disease than those having asfotase alfa (see section 3.9). It also noted that people in the UK MAA (who all had asfotase alfa treatment) were more severely affected than people who had asfotase alfa in the Global Hypophosphatasia Registry. The naive comparative evidence indicated that asfotase alfa improves mobility on the 6MWT, patient-reported pain based on BPI-SF and health-related quality of life compared with people who have not had treatment. The EAG agreed with the company that people in the UK MAA were more severely affected than people in the Global Hypophosphatasia Registry, ENB-006-09/ENB-008-10 and ENB-009-10. However, it also had concerns around the evidence presented by the company. This included inconsistencies in the reporting of baseline data that meant it was unclear if all available participants had been included in the comparative analysis. The EAG noted that, overall, the naive comparative evidence indicates that asfotase alfa improves outcomes more than best supportive care for people with the most severe symptoms at baseline. But, it suggested that there are no clear improvements in outcomes with asfotase alfa compared with best supportive care for people who have less-severe disease. The committee concluded that the evidence presented indicated that asfotase alfa was more effective than best supportive care in the severely affected juvenile-onset population for the outcomes reported, although it noted there was uncertainty based on the inability to perform a matched comparison.

Comparative analysis methods to minimise bias

3.13 The comparative analysis done by the company for both the perinatal- or infantile-onset and juvenile-onset subgroups did not attempt to match people who had asfotase alfa and people in the untreated control group using key

demographic and clinical characteristics. It also did not adjust for potential confounders, meaning there remained uncertainty about whether the treatment and control groups were clinically similar. The company considered the demographic, baseline and hypophosphatasia medical histories of people in the 2 groups to be clinically similar in the perinatal- or infantile-onset subgroup. But the EAG noted there was not enough information provided to make this judgement. The company considered that the baseline disease severity in the juvenile-onset subgroup differed significantly in people treated in ENB-006-09/ENB-008-10, ENB-009-10 or the UK MAA and people untreated in the Global Hypophosphatasia Registry (see section 3.12). The EAG recommended that comparative analyses should be done by adjusting for potential confounders according to the methods described in the NICE technical support document (TSD) 17. During technical engagement, the company explored whether matching between people in the clinical trials and Global Hypophosphatasia Registry data could take place using the 6MWT outcome. It found that the number of people having best supportive care with multiple 6MWT measures was very small. The company found limited patient numbers when considering the use of the Global Hypophosphatasia Registry for mortality (see section 3.9). The company focused its consideration on mortality and 6MWT. This was because these outcomes were important for the economic model (see section 3.14) and were generally better reported in the registry than other outcomes like health-related quality of life. The committee would have liked to see individual patient data used to carry out matched analyses using the methods described in NICE TSD 17 for all relevant outcomes. However, it recognised that the available data may have been too limited for this analysis to be meaningful. It therefore concluded that the comparative analyses presented separately for people with perinatal- or infantile-onset and juvenile-onset hypophosphatasia could be used to inform the economic models for each subgroup.

Economic model

Company's modelling approach

3.14 In HST6, the company developed a Markov model that compared asfotase alfa with best supportive care. It had 6 states: 4 according to the level of severity

defined by 6MWT distance, a state for people who needed invasive ventilation and death (including hypophosphatasia-related and age-related death). For the current review, the company updated the model so that it was structured differently for people aged under 5 years compared with those aged 5 years or over. Those aged under 5 could be in 3 health states: alive with no invasive ventilation, alive with invasive ventilation or death (including hypophosphatasia-related and age-related death). For those aged 5 or over, 4 health states represented increasing levels of disease severity (1 to 4) defined by 6MWT distance or death (age-related death only). The company updated the model to capture the increased risks of ventilation and hypophosphatasia-related mortality in younger people. The EAG was broadly happy with the model structure but flagged that the company's assumption that all people surviving to the age of 5 enter the model in the most severe health state. They noted that not all these people would require invasive ventilation so may not be in the most severe health state. The EAG was also unclear why the company did not use the UK MAA data to inform the baseline cohort characteristics, given the UK MAA data is the source for most of the new data on people who had asfotase alfa included in submission. The model generated results for 2 populations: people with perinatal- or infantile-onset hypophosphatasia and people with juvenile-onset hypophosphatasia. The committee was concerned that the population entering the model when results for a juvenile-onset hypophosphatasia were generated was not based on disease severity in that subgroup. Instead, it was based on paediatric-onset hypophosphatasia more generally. This meant that the juvenile-onset hypophosphatasia may model more severely affected people than expected. This may cause a high proportion of the modelled population to enter the most severe health states over the course of the model. In response to the draft guidance consultation, the company updated its model for the juvenile-onset population to include starting disease severity and transition probabilities based on data from the juvenile-onset population of ENB-009-10 and the UK MAA. The committee concluded that the model structure was generally appropriate for decision making.

Transition probabilities for invasive ventilation in under 5s model cohort

3.15 Transition probabilities for invasive ventilation in both arms came from a study

published by Whyte et al. (2014). A 12-weekly probability of having invasive ventilation of 0.0220 for asfotase alfa and 0.0618 for best supportive care were used in the model. These values were applied as a constant risk between the ages of 0 and 5 years and are age independent. The company stated that this was to capture the potential need for repeated invasive ventilation support. The EAG said that a time-to-event analysis would be more informative provided that repeated ventilation was not needed by many people. The company noted that a time-to-event analysis would not allow people to come off ventilation. The committee considered that people require ventilation for different reasons. Some people will not survive without ventilation and for these people a time-to-event analysis would be reasonable. Other people will go on and off ventilation as needed and for these people a time-to-event analysis would not be reasonable. The committee concluded that whilst there is uncertainty in the transition probabilities for invasive ventilation, the approach taken by the company is broadly reasonable.

Utility values

Source of utility values

3.16 The company used health state utility values that were based on a vignette study rated by UK clinical experts. The same values were used as in the original appraisal, except for people aged under 5 years on ventilation. For this group, utility was changed from -0.09 in the original model to 0.00 in the current model. The EAG said that patient-reported data collected in the UK MAA data or Global Hypophosphatasia Registry should be used to inform the utility values, rather than them being based on expert opinion from the vignette study. The company considered the UK MAA data and noted that there was a lack of utility estimates available in the data for people in the worst severity health states. There were 2 people (4 records) in severity level 2, and 3 people (7 records) in severity level 1. It also said that the utility values for severity level 3 and level 4 were similar to those in the vignette. The committee concluded that in the absence of sufficient data to produce reliable utility values by health state, the use of the vignette results was reasonable.

Carer disutility

3.17 The impact on carer health-related quality of life was included by the company in 2 ways:

- All health states, except the lowest severity level in people aged 5 years and over, included a disutility to account for the impact on carers. Because no data was available for hypophosphatasia, the company used data for Duchenne's muscular dystrophy. This was because it was considered to have a similar burden on caregivers. They used a value of 0.17 for the most severe health state with lower values in the other health states. The EAG updated the disutility in the most severe state to 0.11 because this was the value used in NICE's highly specialised technologies guidance HST3 ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene (published July 2016). The committee was concerned that the use of the values from Duchenne's muscular dystrophy did not fully capture the impact on carers of people with hypophosphatasia. It recognised that events such as seizures, which have a profound impact on carers, are more common in perinatal- or infantile-onset hypophosphatasia than in Duchenne's muscular dystrophy. The clinical experts suggested that the caregiver burden associated with Duchenne's muscular dystrophy may be similar to paediatric-onset hypophosphatasia. But, the caregiver burden varies from person to person and may increase over time as the disease progresses. The company restricted the duration of the disutility so that it only applied for a similar length of time in the 2 groups. This was to avoid the counterintuitive outcome whereby increased survival with asfotase alfa reduced the quality-adjusted life year (QALY) gain because carers experienced this disutility for longer. The EAG noted that this counterintuitive outcome was only applicable in the results for the perinatal- or infantile-onset subgroup because people with juvenile-onset disease were assumed to have background mortality only. The EAG changed the model so that this disutility was applied for as long as care is provided based on survival in each arm, rather than for the same time-period in both arms. The committee agreed with this correction. They considered that the use of the EAG's approach in the model was technically correct but produced the counterintuitive outcome mentioned above. The committee therefore preferred to consider this aspect qualitatively for the perinatal- and infantile-onset populations. For the juvenile-onset population, the committee discussed that the company had not fully justified the use of

the utility value of 0.17. Therefore, it concluded that it was appropriate to use the value of 0.11 used in NICE's highly specialised technologies guidance on ataluren for treating Duchenne muscular dystrophy.

- The impact of infant death on the health-related quality of life of carers was also included by the company in its base case. The EAG noted that this was also only applicable to the perinatal- or infantile-population. A reduction in utility of 0.04 in 2 carers was applied for the remainder of their lives, based on scenario presented by a company, and rejected by the committee, in NICE's highly specialised technologies guidance on Strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency. The EAG noted that the inclusion of disutility to account for bereavement is rare and preferred to include this analysis as a scenario rather than including the impact in the base case. The committee agreed that it would consider the disutility associated with bereavement qualitatively.

Costs

Asfotase alfa cost

3.18 Asfotase alfa has a weight-based dosing regimen. Therefore, the company's model needed the mean weight of the people having asfotase alfa to be estimated to calculate the treatment cost. The company used data from the clinical trials and the UK MAA study to determine mean weight value curves. The curves were then smoothed using a third-degree polynomial model. This resulted in weight estimates that were lower than that of the general population. The company said that this is reasonable because the weight of people under 18 with hypophosphatasia is similar to the 25th percentile of the UK population. In adults the estimated weight was below the UK average. However, the company stated that both the estimated weight and UK average require the same dose of asfotase alfa. So, there is no impact on the drug cost. The EAG considered that only the weight modelled by the company in people aged under 9 years was lower than the 25th percentile of the UK population. So, the EAG did a scenario analysis in which UK general population median weight values were used at all ages. The clinical experts looked at the values used by the company and said

that the company's estimates of weight in children seemed plausible. The committee concluded that the approach taken by the company to model weight was reasonable.

Drug wastage

3.19 The company stated that in clinical practice drug wastage is minimised by rounding down the dose per administration. This is provided the reduction is not more than 3 mg to 4 mg per administration. Based on this, the company's base case accounted for rounding down if the administered dose was 12 mg less than the required weekly dose. The clinical experts agreed that in practice, the dose given may be adjusted from the licenced dose to avoid drug wastage from starting a new vial, if the expected clinical benefits were being achieved. They noted that the level of dose rounding suggested by the company was reasonable based on clinical practice. The EAG took a more conservative approach than the company whereby the number of vials required for a dose was rounded up and any wastage not used. It also presented a scenario analysis including rounding the dose down, as in the company's model. This showed that the impact of including dose rounding on the incremental cost-effectiveness ratio (ICER) was small. The committee considered that dose rounding may be used in practice but that the EAG's approach aligns with the recommended dosage in the summary of product characteristics. They concluded that it was uncertain whether the company or the EAGs approach was appropriate, but that the impact on the cost-effectiveness results is small.

Assumed reduction in price from loss of market exclusivity

3.20 The company originally assumed a reduction in the price of asfotase alfa after 7 years because of patent expiration. The EAG understood the company's justification for this approach but considered that there was no robust basis for making this assumption. The EAG also considered the size of the reduction to be arbitrary. This was discussed at technical engagement and the company agreed to remove this price reduction. At the first committee meeting the company and the EAGs base case both removed the assumption of a reduction in price from loss of market exclusivity. The committee stated that it had not previously

considered price reductions resulting from the potential introduction of generics or biosimilars. This is because it is speculative and the impact of their introduction is unknown. It highlighted that the cost of several other resources included in the company's economic model could change over time. The committee noted that NICE's health technology evaluations: the manual (2022) states that analyses should be based on price reductions when it is known that some form of price reduction is available across the NHS. The committee concluded that the price reduction after 7 years was inappropriate and should not be included in the analysis.

QALY weighting

3.21 The committee understood that NICE's health technology evaluations: the manual (2022) specifies that a most plausible ICER of below £100,000 per QALY gained for a highly specialised technology is usually considered an effective use of NHS resources. For a most plausible ICER above £100,000 per QALY gained, judgements about the acceptability of the highly specialised technology as an effective use of NHS resources must take account of the size of the incremental therapeutic improvement. This is shown by the number of additional QALYs gained and by applying a 'QALY weight'. The committee understood that a weight between 1 and 3 can be applied when the QALY gain is between 10 and 30 QALYs. It discussed the number of undiscounted QALYs in the analysis. The estimated QALY gains are commercial in confidence so cannot be reported here but are substantially above 30 QALYs. Therefore, the committee noted that the undiscounted QALY gains for the scenarios incorporating its preferred assumptions met the criteria for applying a QALY weight. It acknowledged there was uncertainty in the estimates but agreed the extra health and quality-of-life benefits of asfotase alfa are likely to be substantial.

Cost-effectiveness estimates

Cost-effectiveness estimates in perinatal- or infantile-onset hypophosphatasia

3.22 The company's base case resulted in a probabilistic ICER of £74,980 per QALY gained in perinatal- or infantile-onset hypophosphatasia with the QALY weighting applied. The EAG's base-case resulted in a probabilistic ICER of £77,757 per QALY gained in perinatal- or infantile-onset hypophosphatasia with the QALY weighting applied. This includes the confidential discount for asfotase alfa. The committee considered that the assumptions underpinning the EAG's ICER was more closely aligned with its preferred assumptions in people with perinatal- or infantile-onset hypophosphatasia. But, it noted that the EAG's model included carer disutility, which it preferred to consider qualitatively in this population. Although including the carer disutility in the model increased the ICER, the committee agreed that this was appropriate for decision making, but should be acknowledged when also qualitatively considering the carer burden. With the QALY weighting applied, the EAG's ICER was within the threshold normally considered an effective use of NHS resources in a highly specialised technology.

Cost-effectiveness estimates in juvenile-onset hypophosphatasia

3.23 The company's updated base case resulted in a probabilistic ICER of £88,410 per QALY gained in juvenile-onset hypophosphatasia with the QALY weighting applied. The EAG's base-case results at the second evaluation committee meeting resulted in probabilistic ICER of £98,276 per QALY gained in juvenile-onset hypophosphatasia with the QALY weighting applied. The committee considered that the assumptions underpinning the EAG's ICER was more closely aligned with its preferred assumptions in people with juvenile-onset hypophosphatasia. With the QALY weighting applied, this was within the threshold normally considered an effective use of NHS resources in a highly specialised technology.

Other factors

Equality issues

3.24 The company noted that if recommendations differ by age then there could be potential equality considerations. The committee discussed this in light of its recommendations, which do differ by age at onset. However, the committee was clear that this is because the burdens of hypophosphatasia and the evidence it was presented with differ between perinatal- or infantile-onset and juvenile-onset hypophosphatasia. No other potential equality issues were identified by the committee.

Uncaptured benefits

3.25 The patient experts said that asfotase alfa allowed people to regain control of their symptoms, resulting in improved performance in school, and improved work and social life. The company presented a scenario that included the cost of productivity losses associated with hypophosphatasia. The committee did not consider cost savings and benefits incurred outside the NHS to be qualitatively greater than those provided by other similar highly specialised technologies.

Conclusion

Recommendations

3.26 The committee recognised that paediatric-onset hypophosphatasia is rare and can substantially affect the lives of people with the condition, their families and carers. It understood that the only alternative to asfotase alfa is best supportive care, which varies according to the type and severity of symptoms. The committee understood that symptoms vary between people and that the prognosis of hypophosphatasia is more severe in those with perinatal- or infantile-onset hypophosphatasia than those with juvenile-onset hypophosphatasia. The committee considered all evidence presented, and the

opinions of the clinical and patient experts. The committee took into account its preferred assumptions, indirect treatment benefits and other factors. It considered that in people with either perinatal-, infantile- or juvenile-onset hypophosphatasia, the most plausible ICERs were likely to be below the threshold considered to provide value for money in the context of a highly specialised service when the company's confidential discount and QALY weighting was applied. The committee recalled that the people with severe juvenile-onset hypophosphatasia were identifiable from the starting rules included in the MAA from HST6 (see section 3.3). The committee discussed that people with severe hypophosphatasia would be likely to benefit most from asfotase alfa and that the evidence from the UK MAA was based on this population. It therefore agreed that it was appropriate to restrict use of asfotase alfa to this population. So, asfotase alfa is recommended in people with paediatric-onset hypophosphatasia as set out in the original MAA starting criteria from HST6 (see section 3.3).

4 Implementation

4.1 Section 8(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE highly specialised technologies guidance. When a NICE highly specialised technologies guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has perinatal-, infantile- or juvenile-onset hypophosphatasia and the doctor responsible for their care thinks that asfotase alfa is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Peter Jackson
Chair, highly specialised technologies evaluation committee

NICE project team

Each highly specialised technology evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

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