

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 are 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.

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.

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1 Recommendations

1.1 Asfotase alfa is recommended as an option for treating paediatric-onset hypophosphatasia only:

- for people who meet the criteria for treatment within the [managed access arrangement](#) (see [section 4.18](#)), and
- for the duration of this arrangement and in line with the other conditions it specifies, and
- when the company provides asfotase alfa with the confidential commercial terms agreed with NHS England.

1.2 These recommendations are not intended to affect treatment with asfotase alfa that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. For children and young people, this decision should be made jointly by the clinician and the child or young person or the child or young person's parents or carers.

2 The condition

2.1 Hypophosphatasia is a genetic disorder caused by mutations in the tissue non-specific alkaline phosphatase (TNSALP) gene, which reduce its 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 (onset before or at birth)
- infantile onset (onset at 0–6 months)
- juvenile onset (also referred to as childhood-onset; onset between 6 months and 17 years)
- adult onset (onset at 18 years and over) and
- odontohypophosphatasia (only dental symptoms).

Paediatric-onset hypophosphatasia includes everyone with hypophosphatasia of perinatal, infantile, or juvenile onset.

2.2 The signs and symptoms of hypophosphatasia vary widely and can appear any time from before birth to adulthood. These 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. People who present with hypophosphatasia in the first 6 months of life (that is, people with perinatal- or infantile-onset disease) have a high mortality rate. About 50–100% of babies die within the first year of life, primarily because of respiratory failure. Juvenile-onset hypophosphatasia that develops later in childhood is associated with a substantially lower mortality rate than the form that appears in infancy, but is often debilitating and leads to bone deformities that may result in delayed walking, limb weaknesses, skeletal pain and non-traumatic fractures.

2.3 The prevalence of severe forms of hypophosphatasia is unknown in England.

However, in Europe, the rate 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. The evidence submissions NICE received from the company and clinical experts estimated that between 1 and 7 people are diagnosed with perinatal- and infantile-onset hypophosphatasia each year in England.

3 The technology

- 3.1 Asfotase alfa (Strensiq, Alexion Pharma UK) is a targeted enzyme replacement therapy designed to restore the regulation of metabolic processes in the bones and teeth, and to reduce complications of dysregulated bone mineral metabolism. Asfotase alfa is administered by subcutaneous injection.
- 3.2 Asfotase alfa has a marketing authorisation under exceptional circumstances in the UK 'for long-term enzyme replacement therapy in patients with paediatric-onset hypophosphatasia to treat the bone manifestations of the disease'. Treatment should be started by a physician experienced in the management of metabolic or bone disorders. The recommended dosage of asfotase alfa is 2 mg/kg 3 times per week, or 1 mg/kg 6 times per week. For full details of the recommended dosage regimens of asfotase alfa, see the summary of product characteristics.
- 3.3 The summary of product characteristics lists the following very common adverse reactions for asfotase alfa: contusion, erythema, headache, injection-site reactions, irritability, pain in extremity and pyrexia. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 3.4 Asfotase alfa is available in vials of 40 mg/ml and 100 mg/ml. The cost of asfotase alfa is £58.80 per mg (excluding VAT; company's evidence submission). The cost of 52 weeks of treatment, assuming an average weight of 19.3 kg, is £366,912 per patient (excluding VAT). The company has proposed that asfotase alfa will be made available under commercial terms agreed with NHS England (including a price offer, per-patient cost cap and other commercial terms). The details of the commercial terms are commercial in confidence.

4 Evidence submissions

The evaluation committee ([section 7](#)) considered evidence submitted by Alexion, a review of this submission by the evidence review group (ERG) and evidence submitted by clinical experts, patient experts and NHS England.

Nature of the condition

- 4.1 Patient experts and patient groups described how hypophosphatasia can have a profound effect on health-related quality of life.
- For people with perinatal- and 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 health-related quality of life.
 - Functional disability and pain were identified as the most burdensome aspects of juvenile-onset hypophosphatasia that affect health-related quality of life. They highlighted that many children with hypophosphatasia have difficulties with pain and mobility, and are therefore unable to take part in activities such as playing with friends or attending school. The emotional wellbeing of young people with hypophosphatasia may also be affected as they become more conscious of their condition (for example, experts noted that they may have anxiety or depression).
 - Adults with paediatric-onset hypophosphatasia are often unable to work because of mobility problems and the need to have numerous surgical procedures during their lives.
 - There is also a large burden on carers of people affected by hypophosphatasia, particularly carers of babies. There is a significant emotional effect on families because of the high risk of death associated with infantile-onset hypophosphatasia and the difficulty in parents accepting their child's condition. 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). The daily lives of carers 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. This sometimes leads to families relocating.

4.2 For people with perinatal- and infantile-onset hypophosphatasia, treatments that can help prolong survival are of considerable importance; improving health-related quality of life is viewed as a secondary consideration by parents and healthcare professionals. A patient group highlighted that the parents of 1 infant understood that, without asfotase alfa, their child was unlikely to survive to 9 months.

Clinical evidence

4.3 The company did a systematic literature review to identify studies evaluating the clinical effectiveness of asfotase alfa for treating paediatric-onset hypophosphatasia. It found 4 open-label phase II studies of asfotase alfa (2 of which had associated extension studies):

- ENB-002-08, a non-randomised 24-week single-arm study in 11 people of 36 months and under with infantile-onset hypophosphatasia.
- ENB-003-08, an extension study of ENB-002-08 that is evaluating 10 people for up to 5 years.
- ENB-010-10, a non-randomised, dose-comparison study of asfotase alfa treatment for up to 48 months in 59 people of 5 years and under with infantile-onset hypophosphatasia.
- ENB-006-09, a randomised 24-week dose-comparison study in 13 people of 5–12 years with infantile- or juvenile-onset hypophosphatasia.
- ENB-008-10, an extension study of ENB-006-09 that is evaluating 12 people for up to 5 years.

- ENB-009-10, a randomised, 24-week concurrent control study in 19 people of 13–66 years with paediatric-onset hypophosphatasia.

Only ENB-002-08 and ENB-006-09 have finished. The company stated that patients included in the studies of asfotase alfa presented with clinical symptoms that were characteristic of their age at onset of hypophosphatasia and enrolment, and that a broad range of outcome measures were collected across studies to reflect the symptoms of the disease in each age group.

4.4 The company also identified 3 retrospective non-interventional studies:

- ENB-011-10, a retrospective natural history study of babies with severe perinatal- and infantile-onset hypophosphatasia. Data on survival and the need for invasive ventilation were taken from medical records of children up to 5 years.
- ALX-HPP-502, a retrospective natural history study of children with juvenile-onset hypophosphatasia (5–15 years). The study focused on functional assessments of physical abilities, changes in growth (height and weight) and skeletal improvement (severity of rickets).
- ALX-HPP-502s, a single-centre substudy of ALX-HPP-502. Data for additional functional measures were taken from medical records and videos were obtained from a longitudinal natural history database to characterise gait.

4.5 The primary outcome of ENB-002-08 and ENB-010-10 was change in severity of rickets on skeletal radiographs from baseline to week 24, measured by the Radiographic Global Impression of Change (RGI-C) scale. The RGI-C is a 7-point rating scale that ranges from –3 (indicates severe worsening of hypophosphatasia-associated rickets) to +3 (indicates complete or near complete healing of hypophosphatasia-associated rickets). An RGI-C score of +2 or more is considered to be a response to treatment in people with hypophosphatasia. Secondary outcomes included height and weight Z-scores and the number of people needing respiratory support. The Z-score indicates how many standard deviations an infant's height or weight is from the mean of the general population.

4.6 In ENB-002-08, treatment with asfotase alfa resulted in a mean change in RGI-C scores from baseline to week 24 of +1.67 and median change of +2.00 ($p=0.0039$). Most people had an RGI-C score between +2 and +3 (7 out of 11; 63.6%). No patients had an RGI-C score of +3 by week 24 ('complete or near

complete healing'). However, by week 240 of ENB-003-08, all 9 people who had been followed up had an RGI-C score of +2 or more.

4.7 The company provided the results of an interim analysis of 28 people included in ENB-010-10. This analysis suggested that treatment with asfotase alfa resulted in a mean change in RGI-C score from baseline to week 24 of +1.7 ($p < 0.0001$). The company stated that the results of the primary outcome and the secondary outcomes for all 59 patients included in ENB-010-10, as presented in its evidence submission, were academic in confidence and cannot be reported here.

4.8 The company submitted a pre-specified analysis of overall survival for asfotase alfa from people in ENB-002-08, ENB-003-08 and ENB-010-10 compared with an untreated historical control group (ENB-011-10). In this analysis, 4 out of 37 people (10.8%) in the asfotase alfa group had died, compared with 35 out of 48 people (72.9%) in the untreated group during the time period evaluated ($p < 0.0001$). The company presented median survival by diagnosis date. The median number of days from birth until death in the historical control group by year of diagnosis increased over time. The values are academic in confidence and cannot be reported here.

4.9 In response to clarification, the company provided survival analyses adjusted for the following potential biases:

- differences in the year of diagnosis of the historical control group (see section 4.8)
- survival estimated from birth in the historical control group compared with from the start of treatment in people having asfotase alfa.

The company estimated an adjusted hazard ratio by excluding those diagnosed before 2000 and those who died before 38 weeks from the historical control group. The company stated that the adjusted hazard ratio was lower than the estimate for the unadjusted hazard ratio. The adjusted and unadjusted hazard ratios are academic in confidence and cannot be reported here. The company presented the results of a further analysis that was requested by the Committee for Medicinal Products for Human Use. This additional analysis retrospectively matched babies from its historical control data with babies having asfotase alfa from its clinical studies ($n=37$; 29 were considered exact matches). The results of the company's matched analysis are academic in confidence and cannot be reported here.

- 4.10 ENB-006-09 included 13 people randomised to asfotase alfa 2 mg/kg or 3 mg/kg 3 times a week for 24 weeks, and was the only study to include non-concurrent historical control patients selected from a natural history database (n=16). The primary outcome was change in the severity of rickets on skeletal radiographs from baseline to week 24, measured by RGI-C, for asfotase alfa compared with the historical control. Treatment with asfotase alfa resulted in a median improvement in RGI-C compared with the historical control (p=0.0007). Median RGI-C scores for asfotase alfa and the historical control were +2.0 and 0.0 respectively. Nine out of 13 people having asfotase alfa had an RGI-C score of +2 or more (69%) compared with 1 out of 16 people in the historical control group (6.3%; p=0.0010). Improvements in the severity of rickets for asfotase alfa compared with the historical control were maintained until the data cut-off at week 96 of the extension study (ENB-008-10). The company also presented results by age of hypophosphatasia onset but these are academic in confidence and cannot be reported here.
- 4.11 The height, weight and BMI Z-scores, and 6-minute walk test (6MWT) distance results from ENB-006-09 and ENB-008-10 are academic in confidence and cannot be reported here.
- 4.12 The company submitted a comparative analysis of people having asfotase alfa from ENB-006-09 and ENB-009-10 with historical control patients from 3 sources (ALX-HPP-502, ALX-HPP-502s and ENB-006-009/ENB-008-10) for rickets severity, growth and gait outcomes. The results of this comparative analysis are academic in confidence and cannot be reported here.
- 4.13 The results of a 6MWT at baseline and at 24 weeks were available for 13 people in the asfotase alfa group and 4 people in the historical control group of ENB-009-10. The 6MWT results from ENB-009-10 are academic in confidence and cannot be reported here.
- 4.14 The company noted that asfotase alfa is a lifetime therapy and stated that there is no evidence to guide the development of treatment continuation rules. Clinical experts suggested that, once a person's bone health has improved, individualised treatment regimens for maintaining bone health would need to be established (for example, exploring less frequent injections or lower doses).
- 4.15 Health-related quality-of-life data were measured at baseline and several time

points using the Childhood Health Assessment Questionnaire (CHAQ; ENB-006-09 and ENB-008-10), Paediatric Outcome Data Collection Instrument (PODCI; ENB-006-09 and ENB-008-10) and the Lower Extremity Functional Scale (LEFS; ENB009-10). These data are academic in confidence and cannot be reported here.

- 4.16 The company presented EuroQol-5 dimensions survey (EQ-5D) results from its European Patient Survey. The EQ-5D instrument was completed by 10 parents on behalf of their child, and by 25 adults with hypophosphatasia. The mean EQ-5D score for children having asfotase alfa was 0.76 (n=2) and 0.43 in children who did not have asfotase alfa (n=8). The company highlighted that the EQ-5D scores were higher for children with normal walking ability (0.73, n=1) than for children with impaired walking ability (0.56, n=8) or who depended on walking aids (-0.24, n=1). All adults were untreated and had a mean EQ-5D score of 0.39. The company noted that the EQ-5D scores were only slightly higher for adults with normal walking ability (0.51, n=6) than for adults with impaired walking ability (0.48, n=14). The mean EQ-5D score for adults who depended on walking aids was -0.01 (n=5).
- 4.17 The company presented adverse event data for people having asfotase alfa (no data were presented for people who did not have treatment or the historical controls). Median exposure to treatment with asfotase alfa was 1.90 patient years. In a pooled analysis of the interventional studies (excluding ENB-001-08), all people (n=102) had at least 1 adverse event. Most adverse events were considered unrelated to asfotase alfa treatment (2,542 out of 3,676) and were of mild intensity (2,758 out of 3,676). Over 25% of the adverse events were classified as injection-site reactions or injection-associated reactions. Treatment was stopped by 4 people, who withdrew from the studies. A total of 274 non-fatal serious adverse events were reported by 48 people (47.1%). Most of these events were in people with infantile-onset hypophosphatasia (262 out of 274 events). Overall, 8 deaths were reported (1 of which was before treatment started).

Managed access arrangement

- 4.18 The company proposed a managed access arrangement, which was developed with clinical experts and patient groups and revised after advice from NICE and discussion with NHS England. The arrangement was proposed to last 5 years,

and includes defined criteria for starting and stopping asfotase alfa treatment, and monitoring and data collection requirements:

- A national committee made up of experts in hypophosphatasia, pain management and commissioning will discuss all decisions to start or stop asfotase alfa treatment within the managed access arrangement.
- To be considered for asfotase alfa treatment, patients must agree to the terms of the arrangement (including attending regular follow-up clinics and inclusion in the data collection).
- **Starting criteria:** All people with perinatal- and infantile-onset hypophosphatasia, regardless of current age, can start treatment with asfotase alfa. Asfotase alfa can be considered for children (aged 1–4 years and 5–18 years) with juvenile-onset disease if they do not reach motor milestones, have pain with significant disability or have restricted mobility. The drug can also be considered for adults (18 years and over) with juvenile-onset disease if they have 2 of the following: current fractures or a history of fractures characteristic of hypophosphatasia; persistent or recurrent pain with disability; and restriction of mobility.
- **Stopping criteria:** Babies under 1 year with respiratory problems can continue treatment for the duration of the managed access arrangement unless they develop serious adverse events, other life-limiting conditions or remain ventilator dependent after 2 years. Children with juvenile-onset disease will stop treatment if 2 of the 3 stopping criteria are met: loss of height or growth impairment; no improvement in physical function or fall in mobility score; and no reduction in pain. Adults with juvenile-onset disease will stop treatment if 1 of the following criteria are met: no improvement in physical function or fall in mobility score; continued fractures over a 3-year period; and no reduction in pain.
- **Monitoring and data collection:** Data will be collected from everyone who has asfotase alfa within the managed access arrangement, and will be recorded in a dedicated database. The company stated that NHS England will have access to this database for audit and analysis of individual-level data, and will also be provided with relevant data extracts from the global hypophosphatasia registry database to assist in assessing asfotase alfa.

Value for money

4.19 The company submitted a Markov state transition model that compared

asfotase alfa with best supportive care. The company's economic model 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). People who needed invasive ventilation moved to severity IV (that is, the most severe state). The company acknowledged that the 6MWT does not capture all the symptoms of hypophosphatasia (for example, craniosynostosis, severe pain, renal complications). However, the company stated that 6MWT distance was identified by its UK clinical experts as the outcome measure from its trials that most closely reflected the latent severity of disease. The company base-case analysis used a threshold of 17.8% to define a minimal clinically important difference between each severity level (that is, twice the minimal clinically important difference for the 6MWT distance in people with Duchenne muscular dystrophy, which the company stated provided the closest proxy available for people with paediatric-onset hypophosphatasia). The company used a 12-week cycle length, and applied a half-cycle correction to the first and last cycles. The company did the economic analysis from an NHS perspective and chose a lifetime time horizon. Costs and health effects were discounted at an annual rate of 1.5% in the base case; a discounting rate of 3.5% per year was presented in scenario analyses.

4.20 Observations of the 6MWT were available from the trials for 28 people with either infantile- or juvenile-onset hypophosphatasia who had asfotase alfa and best supportive care (ENB-006-09, ENB-008-10 and ENB-009-10). The 28 people had at least 2 assessments of 6MWT distance, and their baseline age of hypophosphatasia onset ranged from 0 to 4.0 years (mean 1.3 years). For these 28 people, there were 250 observed transitions for people having asfotase alfa and 34 observed transitions for people having best supportive care. The company stated that between each 12-week visit, the average distance walked:

- improved by 11.6 m and 1.35 percentage points in per cent predicted in people having asfotase alfa and

- decreased by 13.6 m and 3.91 percentage points in per cent predicted in people having best supportive care.

Their baseline age at the first trial visit ranged from 5.9 years to 59.3 years (mean 26 years). To estimate the transition probabilities between each of the 6MWT severity levels in the economic model, the company used an ordered probit regression model that controlled for age and the days elapsed between healthcare visits. The distributions for the baseline level of severity were based on clinical trial data.

- 4.21 Hypophosphatasia-related deaths and invasive ventilation occurred in the company's model at the same time at which they were seen in the trials (ENB-002-08, ENB-003-08, ENB-010-10 and ENB-011-10). The company's base-case analysis used a mean starting age of 5.8 years (average age across the trials). Therefore, in the company's base case, there was no risk of hypophosphatasia-related deaths or invasive ventilation because none of these events were seen in the trials in people 5 years and over. The company explored different starting ages and levels of severity in scenario analyses.
- 4.22 Drug costs for asfotase alfa were based on its list price and the confidential commercial terms, using the recommended dosage in the summary of product characteristics. The company initially assumed that the list price for asfotase alfa reduced by 30% after 10 years because of a loss of data exclusivity (this assumption was removed in later analyses). The company took unit cost data for monitoring and managing hypophosphatasia from NHS reference costs 2013–14, the Personal Social Services Research Unit and the Royal Manchester Children's Hospital. Healthcare resource use estimates for managing each severity level were based on clinical expert opinion. Mean utility values included in the company's economic model were estimated by 9 clinical experts who completed the EQ-5D-5L for vignettes for each severity level state. Annual costs and utility values for each 6MWT state are presented in table 1. The company excluded costs and disutility values associated with adverse reactions because it considered that asfotase alfa was well tolerated and most adverse reactions were mild to moderate in severity.

Table 1 Summary of the company's costs and utility values for each health state

Health state	Annual cost	Utility value
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Base case		
Severity level I	£1,399	0.86
Severity level II	£3,976	0.67
Severity level III	£5,846	0.54
Severity level IV	£14,358	0.23
Scenario analysis (when starting age is below 5 years) ¹		
Invasive ventilation	£399,467	-0.33
¹ No patients aged 5 years and over needed invasive ventilation in the asfotase alfa studies.		

- 4.23 The company presented the results of its cost–consequence analysis for asfotase alfa compared with best supportive care. Total costs and incremental costs for asfotase alfa compared with best supportive care for all analyses are commercial in confidence so cannot be reported here. In the company's base case (discounting rate of 1.5%), asfotase alfa was estimated to produce an additional 25.04 quality-adjusted life years (QALYs) compared with best supportive care (37.53 total QALYs with asfotase alfa, 12.48 total QALYs with best supportive care). With a discounting rate of 3.5%, asfotase alfa was estimated to produce an additional 14.25 QALYs compared with best supportive care.
- 4.24 The company explored parameter and structural uncertainties in its economic model in a 1-way sensitivity analysis, scenario analyses and a probabilistic sensitivity analysis. The 1-way sensitivity analysis suggested that the results were most sensitive to the discounting rate used for costs and health effects, and changes to the utility values. In the probabilistic sensitivity analysis (based on 500 simulations), asfotase alfa treatment produced an additional 18.4 QALYs compared with best supportive care (compared with 25.04 QALYs in the corresponding deterministic analysis). Incremental costs are commercial in confidence and cannot be presented here.
- 4.25 The company presented results for subgroups based on the age at which treatment began, and for additional scenario analyses in which the population baseline characteristics (age and disease severity) were adjusted to match those of people for whom asfotase alfa would be considered under the proposed managed access arrangement. Incremental costs are commercial in confidence

and cannot be presented here; incremental QALYs are shown in table 2. Adjusting the baseline characteristics to match the managed access arrangement population increased the expected QALY gain (compared with the base case). This reflected the expectation that the arrangement would identify the people with more severe hypophosphatasia who would therefore benefit more from treatment with asfotase alfa. The company stated that, in adults with juvenile-onset hypophosphatasia, the QALY gain with asfotase alfa decreased as the age at which treatment started increased.

Table 2 Results of the company's cost–consequence analysis with baseline characteristics adjusted to match the managed access arrangement population

	Perinatal and infantile onset	Juvenile onset			
		0–4 years	5–11 years	12–17 years	18 years and over
Incremental QALYs	18.21	16.66	15.64	15.19	13.47

This analysis is based on a discounting rate of 3.5%. The company also presented results with a discounting rate of 1.5%; these results are not reproduced here.

Abbreviation: QALYs, quality-adjusted life years.

Cost to the NHS and personal social services

4.26 The company explained that limited information was available for estimating the prevalence and incidence of hypophosphatasia in England. With no national statistics available, the company used the incidence rates for paediatric-onset hypophosphatasia from a German study by Beck et al. (2003) and applied them to the population in England in its base-case budget impact model. Beck et al. estimated that the incidence of hypophosphatasia was 0.8 per 1,000,000 in children younger than 1 year and 2.8 per 1,000,000 in children younger than 18 years. To estimate the prevalent population in England in people 18 years and over, the company assumed a life expectancy of 81 years and applied the incidence for children younger than 18 years from Beck et al. Therefore, the company estimated that the numbers of people with paediatric-onset hypophosphatasia in England were 1.9, 149.4 and 553.5 in people aged 0–1 year,

1–17 years, and 18 years and over respectively. The company considered that the rates of diagnosis of paediatric-onset hypophosphatasia would increase if asfotase alfa was used in the NHS, and that uptake of treatment would be higher in younger populations.

- 4.27 The company presented the results of a budget impact analysis over 5 years. It calculated the drug costs for asfotase alfa based on a weighted average for the weights and ages of patients taking part in the clinical trials. The company initially assumed an 80% rate of adherence, with a 100% rate of adherence explored in a scenario and subsequent analyses. The company estimated the number of people for whom treatment would be considered within the managed access arrangement, taking into account published data from the US (Whyte et al. 2015) and surveys of expert centres in the UK. The company subsequently submitted a revised budget impact model, using the latest available evidence on population size, taking into account additional patients identified during the consultation period and including the commercial terms agreed with NHS England. The results were presented for the whole population and broken down by age of disease onset. The estimated budget impact of asfotase alfa is commercial in confidence and cannot be reported here.

Evidence review group review

Clinical evidence

- 4.28 The ERG did not believe any relevant studies were missed by the company's searches.
- 4.29 The ERG stated that conclusions about the treatment effect may be confounded because some of the studies did not include a control group (limiting the robustness of the efficacy data). For the asfotase alfa prospective studies without a concurrent control group, and the ERG considered it reasonable to compare the asfotase alfa data with natural history data to provide a historical control group. However, the ERG considered that each of the comparative analyses was at high risk of bias in favour of asfotase alfa.
- 4.30 For the company's comparative analysis of overall survival in people with infantile-onset hypophosphatasia, the ERG noted that the results were biased in favour of asfotase alfa for 2 reasons:

- **Year of diagnosis:** Despite no disease-modifying treatment, the company showed that the probability of survival for people with infantile-onset hypophosphatasia had improved over the years. Of the historical control group, 13 people were diagnosed before 1990, 14 between 1990 and 1999, and 21 after 2000. All 11 people having asfotase alfa were diagnosed after 2005.
- **Age at enrolment:** The historical control group probably included more people younger than 1 month and younger than 1 week (people with hypophosphatasia younger than 1 month are at higher risk of death than older people) than the asfotase alfa group.

- 4.31 The ERG considered that the lower mean age and lower age of hypophosphatasia onset in the historical control group may bias the results of ENB-006-09 in favour of asfotase alfa. However, it considered that the patient populations were more comparable in this analysis than the populations included in the other 2 comparative analyses provided by the company.
- 4.32 The ERG agreed that people having asfotase alfa in the company's comparative analysis of people with juvenile-onset hypophosphatasia showed clear improvements in skeletal structure, growth and gait compared with the historical control and the pre-treatment group. The ERG commented that, without data for several important baseline characteristics, it was unclear whether the groups were comparable. Therefore, the precise benefit of asfotase alfa treatment was not clear.
- 4.33 The ERG stated that, although there is considerable follow-up in some of the asfotase alfa studies, it was only a fraction of the expected lifetime treatment as proposed by the company. The ERG explained that it cannot be expected that a treatment works equally well or even at all in all people, and stated that the effectiveness of treatment may diminish over time. The ERG concluded that the long-term efficacy and safety of asfotase alfa was uncertain, and that stopping rules for asfotase alfa should be considered given the many differences among people with paediatric-onset hypophosphatasia.

Value for money

- 4.34 The ERG emphasised that the 6MWT does not capture all of the symptoms of hypophosphatasia, nor does it capture all of the important domains of health-related quality of life as measured by the EQ-5D, such as mental health and pain. The ERG considered that the company should have submitted separate models

for people under 5 years and for people 5 years and over because the symptoms of hypophosphatasia and the effect of asfotase alfa are different in these populations.

- 4.35 The ERG noted that the company used an annual discounting rate of 1.5% in its base-case analyses, rather than the 3.5% rate specified in the reference case, and explored whether there were circumstances that might justify using this rate in this case. It described the evidence around whether asfotase alfa restored people who would have died or who would have had a very severely impaired life to full or near full health, and the long-term effects of treatment. The ERG acknowledged that the company's economic model indicated that more people would be in the least severe health states, but questioned the extent to which this could be considered 'full health' and whether the treatment effect would be maintained for their lifetime.
- 4.36 The ERG stated that the transition probabilities estimated by the company's probit model for best supportive care were associated with considerable uncertainty because of the very limited number of 6MWT observations for people having best supportive care. It noted that the company's chosen covariates in the probit model (age, time since previous visit) may not fully reflect the disease severity progression. Therefore, the ERG considered it would have been more appropriate for the company to estimate the transition probabilities with a single probit model controlled for treatment effect rather than with separate probit models for the asfotase alfa and best supportive care groups. The ERG was further concerned that the company's chosen transition probabilities were from a population of people 5 years and over, and that the transition probabilities for younger patients relied on backwards extrapolation, which was not validated (particularly because credible reference 6MWT distances are not available for people younger than 3 years).
- 4.37 The ERG noted that it was not clear how the baseline age and severity levels in the base case were derived or whether they reflected a UK paediatric-onset hypophosphatasia population.
- 4.38 The ERG noted that the company's unadjusted approach for estimating survival and the need for invasive ventilation in the economic model may have been biased:

- The historical controls included people from the time of diagnosis, whereas clinical studies can only include people who survive to study enrolment.
- There were differences in the year of diagnosis.
- The survival curves were estimated from birth rather than from the start of treatment.

The ERG highlighted that the survival analyses provided by the company in response to a request for clarification showed that the company's method of estimating survival in the economic model was potentially biased. The ERG concluded that the company should have attempted to match the populations between asfotase alfa and best supportive care and taken into account the age at enrolment and year of disease when estimating survival in its economic model.

- 4.39 The ERG highlighted the company's assumption of a reduced price for asfotase alfa after 10 years because of a loss of data exclusivity (in the company's initial analysis), and presented exploratory analyses in which this price reduction was removed. The ERG also queried whether the size of the reduction was not reasonably justified by the company. This assumption was removed in the company's later analyses. The ERG noted that the company did not include costs associated with personal social services.
- 4.40 The ERG felt that it was a limitation that utility values were from clinical experts rather than from the clinical studies. It noted that the face validity of the utility values obtained by the experts for each of the health states seemed quite reasonable. However, the company's vignettes assumed strong correlation among all dimensions of health, which may lead to underestimation of the true variation in health-related quality of life within each health state.
- 4.41 The ERG presented the results of an exploratory analysis that:
- estimated the transition probabilities using a single probit model for both asfotase alfa and best supportive care, and controlled for treatment effect (see section 4.35)
 - estimated the survival and need for invasive ventilation in a matched population using a parametric model (the ERG explored 6 distributions and selected the Gompertz distribution as the best fit based on tests of internal and external validity)
 - only used historical control survival data from people who were diagnosed after 2000

- excluded the price reduction for asfotase alfa after 10 years
- discounted the costs and health effects at an annual rate of 3.5%.

This analysis did not include adjustment of the baseline characteristics to match the managed access arrangement population. Total costs and incremental costs for all analyses are commercial in confidence so cannot be reported here. The ERG estimated that asfotase alfa would produce an additional 14.13 QALYs compared with best supportive care (21.59 total QALYs with asfotase alfa, 7.46 total QALYs with best supportive care). The ERG also presented the results of this analysis in subgroups based on the age at which treatment began (table 3).

Table 3 Results of the ERG's exploratory cost–consequence analysis grouped by the age at which treatment began

	Company base case (3.5% discounting rate; see section 4.23)	ERG exploratory analysis					
		Overall population	Perinatal and infantile onset	Juvenile onset			
				0–4 years	5–11 years	12–17 years	≥18 years
Incremental QALYs	14.25	14.13	15.6	14.7	14.2	14.1	9.8

Note: This analysis is based on the original population baseline characteristics – that is, the baseline characteristics have not been adjusted to match the managed access arrangement population.

Abbreviation: ERG, evidence review group; QALYs, quality-adjusted life years.

4.42 The ERG did an additional exploratory analysis for younger people with paediatric-onset hypophosphatasia (starting age of 0). For this analysis, the ERG developed a new model structure with 2 health states: alive and dead. Patients who were alive could also have invasive ventilation. The ERG considered that an alternative model structure was appropriate given the differences in the symptoms of hypophosphatasia and the effect of asfotase alfa for this population compared with the company's base-case population (mean age of 5.8 years). The ERG stated this was supported by the differences between rates for mortality and the need for invasive ventilation. This ERG exploratory model included people from birth and used a time horizon of about 5 years. Total costs

and incremental costs for asfotase alfa compared with best supportive care for all analyses are commercial in confidence so cannot be reported here. At a discounting rate of 3.5%, the ERG estimated that asfotase alfa was estimated to produce an additional 0.91 QALYs compared with best supportive care for younger people over the 5-year time horizon (2.46 total QALYs with asfotase alfa, 1.55 total QALYs with best supportive care). When combining this with the ERG's estimate of cost and consequences beyond 5 years (obtained by applying the ERG's preferred model assumptions to the company model), the ERG estimated a lifetime QALY gain of 13.92 when treating hypophosphatasia in people from birth. The ERG emphasised that its exploratory model for younger people was simple and based on the little evidence available. Therefore, the ERG stated that the results should be interpreted with caution.

Cost to NHS and personal social services

- 4.43 The ERG noted that several of the parameters used in the company's budget impact analysis were the same as those in the cost-consequence model, and that the same limitations would apply to both. However, it noted that the assumptions such as the discounting rate and drop in asfotase alfa price after 10 years were not relevant in the context of the 5-year budget impact analysis. The ERG considered the assumptions made by the company in the initial budget impact analysis to be reasonable.
- 4.44 Full details of all the evidence are in the submissions received for this evaluation, and in the ERG report, which are all available in the [committee papers](#).

5 Consideration of the evidence

The evaluation committee reviewed the data available on the benefits and costs of asfotase alfa, having considered evidence on the nature of paediatric-onset hypophosphatasia and the value placed on the benefits of asfotase alfa by people with the condition, those who represent them, and clinical experts. It also took into account the value for money that asfotase alfa represents and the effective use of resources for specialised commissioning.

Nature of the condition

5.1 The committee discussed the nature of paediatric-onset hypophosphatasia. It understood that hypophosphatasia was a rare, serious and heterogeneous genetic condition associated with considerable morbidity that severely affects the quality of life of people with the condition and their families. The committee heard from the clinical experts that the signs and symptoms of paediatric-onset hypophosphatasia vary widely and can appear any time from birth throughout childhood. The condition is sometimes not diagnosed until adulthood. The clinical experts considered that perinatal- and infantile-onset hypophosphatasia were more severe forms of paediatric-onset hypophosphatasia than juvenile-onset hypophosphatasia. They explained that perinatal- and infantile-onset hypophosphatasia are associated with significant mortality (up to 100%). They also explained that the severity of juvenile-onset hypophosphatasia was more variable in clinical practice because some people were asymptomatic and had normal functioning, but others had significant problems with pain, growth, mobility, bone strength and activities of daily living. The committee heard from the patient experts that, for babies, treatment with asfotase alfa could enable them to have a good quality of life, go on to attend school and make friends, but without it they would not survive. A patient expert highlighted that their 12-year old child, who was diagnosed at 2 years, had pain and needed several medicines every day before getting out of bed. The patient expert emphasised that, on some days, their child feels so low that they do not want to get out of bed. Therefore, the condition has had a substantial effect on the family's emotional wellbeing as well as their child's. The committee understood from the patient expert that, if treatment with asfotase alfa could make juvenile-onset hypophosphatasia more manageable and reduce the need for hospital admissions (for example, for fractures), it would provide benefits to people with the condition and their families. The committee concluded that paediatric-onset

hypophosphatasia is a rare, serious, life-threatening and debilitating condition.

- 5.2 The committee discussed the natural history of paediatric-onset hypophosphatasia. It appreciated that mortality was extremely high in perinatal- and infantile-onset hypophosphatasia. The committee agreed that the natural history of perinatal- and infantile-onset hypophosphatasia over the first 2 years of life was well understood, and that real-world experiences had highlighted the urgent need for an effective treatment option for these babies so that they survive into childhood. The committee went on to consider the natural history of juvenile-onset hypophosphatasia. It heard from the clinical experts that the natural history of juvenile-onset hypophosphatasia was less well understood, and that many patients had been lost to follow-up after 1 or 2 visits because of a lack of effective treatment. It further heard from the clinical experts that symptoms were highly variable among people with juvenile-onset hypophosphatasia, and could even vary significantly within the same patient over time. The committee understood from the clinical experts that fractures and skeletal problems are common in later life but their occurrence and frequency fluctuated within individuals and the population as a whole. It heard that the life expectancy for people with juvenile-onset disease is unclear but is expected to be near normal, with any additional risk of mortality resulting from a higher incidence of multiple and recurrent fractures. The committee concluded that the natural history of paediatric-onset hypophosphatasia was well-defined for the early years of perinatal- or infantile-onset disease, but was not entirely clear for juvenile-onset disease (and is particularly variable in people whose condition is not diagnosed until they are adults).
- 5.3 The committee discussed the current treatment options and management of paediatric-onset hypophosphatasia. It was aware that there was no NICE, NHS England or national guidance for managing paediatric-onset hypophosphatasia. The committee also understood from the patient expert statements that the time taken to diagnose the condition can vary significantly. The committee heard from the clinical experts that supportive care, which aims to monitor and alleviate symptoms, is the current mainstay of treatment. They explained that the goals of treatment for babies with perinatal- and infantile-onset hypophosphatasia were to manage craniosynostosis, prevent seizures, reduce the need for respiratory support (up to 90% of untreated babies need invasive ventilation) and prevent mortality. For people with juvenile-onset hypophosphatasia, the goals of treatment were to reduce and prevent pain,

improve mobility and improve their ability to take part in activities of daily living. The committee concluded that a treatment which meets these goals would be highly valued because there are currently no treatments available that specifically prevent or delay the progression of hypophosphatasia.

Impact of the new technology

5.4 The committee acknowledged the patient experts' view that asfotase alfa offered a lifeline for babies with paediatric-onset hypophosphatasia, who would otherwise die. It heard from the clinical experts that, because asfotase alfa was the first therapy that specifically targets the underlying cause of hypophosphatasia, they considered it to be a step change in the management of paediatric-onset hypophosphatasia.

5.5 The committee discussed the results for overall survival in perinatal- and infantile-onset hypophosphatasia. It noted that the evidence review group (ERG) considered the company's original unadjusted analysis of overall survival to be potentially biased in favour of asfotase alfa compared with the natural history data because of differences in the year of diagnosis and age at enrolment between the groups. The committee was aware that the company had provided an analysis of overall survival that adjusted for these potential biases, which had reduced the size of the treatment benefit. In contrast, a clinical expert highlighted to the committee that the analyses of overall survival may also be biased in favour of the natural history group because 7 of the 12 sites in ENB-011-10 were in the US and Canada. The clinical expert explained that historically the influences of reimbursement in the US and Canada may have produced greater use of invasive ventilation in babies than was typical in England. However, the committee was also told that, more recently, the use of invasive ventilation for babies has become more widespread in the UK, but there was no consensus on this point. The committee heard from the company and clinical experts that, although outcomes in neonatal intensive care have improved over time, invasive ventilation would still remain futile for many people with perinatal- or infantile-onset hypophosphatasia if asfotase alfa were not available. After consideration, the committee agreed that it was more appropriate to use more recent data for the natural history group of babies (that is, those diagnosed in 2000 or after), and to ensure baseline characteristics (for example, age) that influence prognosis are similar in the 2 groups when comparing overall survival data for asfotase alfa with best supportive care. The

committee acknowledged that, even if the available survival data could be adjusted for all potential biases, the probability of survival would almost certainly be higher for people having asfotase alfa compared with people not having asfotase alfa. It concluded that asfotase alfa improved the probability of survival in perinatal- and infantile-onset hypophosphatasia compared with best supportive care.

- 5.6 The committee considered the robustness of the results from the company's trials for asfotase alfa, noting that most of the company's prospective clinical trial evidence did not include a concurrent control group. It agreed that, without a concurrent control group, it was reasonable in the circumstances for the company to compare with natural history data (that is, a historical control group). The committee was aware that data on baseline characteristics were not available for some of the natural history data. It acknowledged that each of the company's comparative analyses risked bias and was subject to considerable uncertainty. The committee concluded that, given the heterogeneous nature of the condition and the trial designs used, the available clinical evidence did not provide either a robust estimate of the size of the benefit or a strong indication of the likely variation in the treatment effect.
- 5.7 The committee discussed the other results of the asfotase alfa clinical trials for paediatric-onset hypophosphatasia. It accepted that the trials of perinatal- and infantile-onset hypophosphatasia generally showed improvements with asfotase alfa treatment across several important outcomes such as the need for respiratory support, severity of rickets and growth. It also noted that improvements were generally seen with asfotase alfa in the company's trials of juvenile-onset hypophosphatasia across several important outcomes such as growth, mobility and pain. The committee concluded that the results of the trials generally suggested that asfotase alfa was associated with clinically meaningful improvements when compared with baseline.
- 5.8 The committee considered the dosage of asfotase alfa. It noted that the recommended dosage in the summary of product characteristics is 2 mg/kg 3 times per week, so was aware that the amount of asfotase alfa used would increase as people get older and gain weight. The committee heard from the clinical experts that some children and adults with hypophosphatasia may need doses higher than that in the marketing authorisation to have a response. It also heard that the trials of asfotase alfa were relatively short in duration, so

registries would be needed to monitor and subsequently guide decisions around whether the dose could be reduced. The committee accepted that, because it had not been formally studied, there was little information around the efficacy of giving a lower dose of asfotase alfa in people whose condition had a sustained response. The committee noted that the overall cost of treatment with asfotase alfa may be reduced if a safe dose reduction regimen could be implemented; however, the current lack of evidence on which to plan a dose reduction regimen adds to the uncertainty about the expected costs of treatment.

Managed access arrangement

- 5.9 The committee discussed how asfotase alfa would potentially be used in clinical practice, and considered in detail the proposed managed access arrangement for asfotase alfa.
- 5.10 The committee heard from the clinical experts that, in principle, the decision to treat babies with perinatal- and infantile-onset hypophosphatasia with asfotase alfa could be based on clinical judgement and would depend on the overall clinical picture. However, in practice, the clinical experts would give asfotase alfa to all babies with perinatal- and infantile-onset hypophosphatasia straight away because, without treatment, most babies would die. The committee heard from clinical experts that they would only consider a dose reduction or stopping treatment once the child came off invasive ventilation and their condition had stabilised (generally supported by improved bone health because of better mineralisation). It heard that there remained uncertainty about how long treatment was likely to be appropriate after stabilising the condition in clinical practice. The committee was aware that juvenile-onset hypophosphatasia has a more variable overall clinical picture than infantile-onset disease, and that some people were functioning normally. It heard from the clinical experts that the decision to start treatment in children or adults could be based on the impact of the condition on their health-related quality of life (such as severity of pain, level of mobility and risk of fracture) and activities of daily living (such as going to school, playing with friends). The committee heard that the clinical experts estimated that around 10% of people with juvenile-onset hypophosphatasia would need treatment at any one time. The clinical experts further stated that, if the condition did not respond after 1 year of treatment (for example, no reduction in pain, or improvements in mobility and health-related quality of life), they would consider stopping asfotase alfa in clinical practice. The committee

heard from the patient experts that parents or carers of children with hypophosphatasia would trust the judgement of the treating clinician on whether asfotase alfa could be reduced or stopped. A patient expert emphasised that this was only if their child had a good quality of life and was regularly tested. The committee accepted that all babies with perinatal- and infantile-onset hypophosphatasia should be treated with asfotase alfa. It understood that the need for treatment in children and adults with juvenile-onset disease was more variable, and that the decision could be based on the impact of the condition on quality of life. The committee further understood that it would be appropriate to consider the need to continue asfotase alfa based on the response to treatment.

- 5.11 The committee noted that the final managed access arrangement proposed detailed criteria for starting and stopping asfotase alfa (see [section 4.18](#)). It understood that the criteria had been refined following previous versions of the managed access arrangement, with input from clinical experts and patient groups, and had been considered by NHS England's clinical panel. The committee considered that the proposal that all babies with perinatal- or infantile-onset disease would be treated with asfotase alfa was consistent with the view that these patients had the greatest clinical need and that most of these patients would benefit from treatment (see [section 5.10](#)). The committee considered that the babies with the most severe, life-threatening disease, for whom treatment is the most urgent, would be very likely to be identified at an expert centre very soon after disease onset, and understood that treatment could be started immediately. The committee also noted that the starting and stopping criteria for children and adults with juvenile-onset disease included a mix of quantitative criteria with defined cut-off values and broader measures of the effect of disease and treatment on quality of life. It heard from the clinical expert that the criteria were thorough and would be expected to identify people who have the greatest clinical need for asfotase alfa and who would benefit the most from treatment. The committee recalled that it had previously expressed concerns that the starting and stopping criteria in previous drafts of the managed access arrangement might not be fully objective in some cases, and that this may be a particular problem for adults because their clinical need is most variable. It considered that the finalised criteria were more robust and objectively defined. The committee concluded that the starting and stopping criteria in the managed access arrangement were appropriate.

- 5.12 The committee noted that treatment decisions within the managed access arrangement would be made by a national committee comprised of experts in hypophosphatasia, pain management and commissioners. It welcomed the inclusion of the national expert committee, and emphasised the value of the multidisciplinary approach in this situation. The committee emphasised the importance of robust governance procedures within managed access arrangements, and was reassured that the expert committee would help ensure the starting and stopping criteria were robustly and objectively applied.
- 5.13 The committee discussed the proposed data collection methods presented within the managed access arrangement. It understood that the data collected through the managed access arrangement would be collated in a dedicated database managed by the company. It also understood that this database would be available to NHS England for independent audit and analysis of individual-level data. The committee applauded this approach to making data available for independent scrutiny. It heard from the company that clinicians would have access to data from people under their care, and was reassured that this would provide an additional level of checking to ensure the quality and accuracy of the data. The committee heard from the company that data collection and data sharing agreements had been prepared, and that statistical analyses would be defined once patient numbers were known. It emphasised that best practice would be to agree and specify the data analyses in advance. It understood that procedures had been defined to minimise and address missing data. The committee further emphasised the importance of careful governance of the data collection, and was reassured by the company that the data would be subject to verification, quality control and audit with a degree of oversight comparable to a clinical trial. The committee concluded that the data collection element of the managed access arrangement was likely to provide valuable evidence to support a review of the guidance at the end of the managed access arrangement period.
- 5.14 In addition to the data collected within the managed access arrangement, the committee queried what evidence would be collected for people who do not have treatment with asfotase alfa – that is, as a comparator. It heard from the clinical expert and the company that the global hypophosphatasia registry was ongoing. The company highlighted that this registry was set up as part of its regulatory commitments, and so was separate from the managed access arrangement, and that it would provide evidence from hundreds of people with

hypophosphatasia worldwide, including those not treated with asfotase alfa. The committee also heard that clinicians would try to collect further information from people who stop asfotase alfa treatment or withdraw from the managed access arrangement. The committee considered that these sources were likely to provide useful comparative data to support future review of the guidance.

- 5.15 The committee noted that the managed access arrangement included a number of detailed assessments and commitments, and was mindful that this might impose a burden on people having asfotase alfa treatment and the treating centres. It heard from the patient expert that people with severe hypophosphatasia and their families were very keen to have treatment with asfotase alfa and understood and accepted the need to collect information as part of the managed access arrangement. It also heard that support would be provided by the patient group. The company explained that further options were being explored to simplify the process and minimise the burden, including telephone or online completion of quality-of-life questionnaires. The committee recalled that it had been reassured that clinicians would have access to the data collected through this route, for people under their care, as an additional check of data quality (see section 5.13). The committee heard from the clinical expert that the highly specialised centres in which treatment would be given were well set up to manage the data collection requirements. The committee was reassured that the managed access arrangement would not impose an undue burden on people with hypophosphatasia or the NHS.

Cost to the NHS and personal social services

- 5.16 The committee discussed the cost of asfotase alfa. It noted that, at list price, the total cost per person per year of treatment with asfotase alfa is £366,912 (assuming an average weight of 19.3 kg and 100% adherence). The committee highlighted that the dosage of asfotase alfa was based on a person's weight, therefore the cost per person is higher for older people, and would increase during a person's lifetime. The committee heard evidence from clinical experts that those with hypophosphatasia are typically slightly below average weight for their age. The committee noted that the company and NHS England had agreed that asfotase alfa would be made available under confidential commercial terms; the details of these terms are commercial in confidence and cannot be reported here.

- 5.17 The committee considered number of people who would have asfotase alfa treatment within the managed access arrangement. It understood that the company had estimated the population size taking into account assumptions about the increase in diagnosis of paediatric-onset hypophosphatasia after asfotase alfa becomes available and the likely rates of eligibility for the managed access arrangement. The anticipated increase in diagnosis was supported by the clinical experts, who stated that clinical practice may change with the availability of an active treatment. The committee was aware that juvenile-onset hypophosphatasia is variable in its severity and may be diagnosed retrospectively in some adults in clinical practice. The committee understood from the clinical experts that it was therefore difficult to estimate the number of people with juvenile-onset hypophosphatasia in England. The committee also recognised that it was difficult to reliably estimate the number of people who would meet the criteria for treatment within the managed access arrangement, and highlighted the wide range between the estimates presented during the evaluation. The committee heard from clinical experts that they considered children with juvenile-onset hypophosphatasia who had the greatest clinical need would all have been previously identified at the expert centres, and was reassured that the number of children currently being treated who would meet the starting criteria in the managed access arrangement was well known. However, the committee emphasised that there were still uncertainties in the number of children who would be treated in future, during the course of the managed access arrangement. The committee heard from NHS England that the largest uncertainties concerned the number of adults who would be treated within the managed access arrangement. The committee considered that the refined starting and stopping criteria in the finalised managed access arrangement, along with elements of the commercial terms, managed the risks associated with the remaining uncertainty in the number of people who would have asfotase alfa treatment within the managed access arrangement.
- 5.18 The committee was aware that, in the initial base case, the company had assumed that adherence to asfotase alfa was 80%, with scenarios exploring 100% adherence. The committee heard from the company that it had based its base-case adherence rate on the upper limit of those rates reported for subcutaneous tumour necrosis factor alpha inhibitors. However, the clinical and patient experts both considered that the company's assumption was not appropriate. The committee heard from the company that parents of children with the condition will either administer asfotase alfa themselves, or ensure

that the drug is taken by the person with the condition. The committee concluded that the scenarios that assumed 100% adherence were more plausible and provided the most appropriate estimates for the budget impact of asfotase alfa.

- 5.19 The committee discussed the overall budget impact of asfotase alfa. It considered the total cost of asfotase alfa for the whole managed access arrangement population and for the different forms of hypophosphatasia (that is, perinatal and infantile onset, children with juvenile onset and adults with juvenile onset), taking into account the commercial terms. These results were commercial in confidence and cannot be reported here. The committee concluded that the confidential commercial terms substantially reduced the cost of asfotase alfa to the NHS and reduced the financial risk, compared with previous proposals.
- 5.20 The committee considered the cost of asfotase alfa in the context of costs incurred by the company for research, development and manufacturing. The committee asked the company to explain the cost of treatment. It heard from the company that the cost of asfotase alfa is driven by the need to recoup the high costs of research, development, manufacturing and marketing of a treatment to be used only by a small number of people, and reflects the long-term benefits associated with asfotase alfa treatment for a condition that severely affects a person's health-related quality of life. The committee acknowledged that developing orphan and ultra-orphan treatments was associated with challenges that were different from those for treatments for bigger patient populations. It recognised the challenges in making a reasonable return on investment for treatments for very rare conditions. The committee also considered the cost of asfotase alfa in the context of NHS highly specialised services. It was aware that NHS England has a single budget for specialised services of approximately £16 billion, which covers highly specialised services and high-cost drugs, as well as a range of other treatments and specialised services. On balance, the committee concluded that, although asfotase alfa was still a very high-cost technology, with the commercial terms agreed with NHS England, the total cost to the NHS was acceptable and manageable in the context of a highly specialised service.

Value for money

5.21 The committee discussed the company's model structure for the cost-consequence analysis. It was aware from the company and the ERG that the health states were based on the level of severity defined by 6-minute walk test (6MWT) distance. The committee understood that the 6MWT did not capture all the symptoms of hypophosphatasia, or the important domains of the EuroQol-5 dimensions survey (EQ-5D) questionnaire (such as pain and mental health), although clinicians may have taken these into account when providing utility values for the illustrative vignettes. The committee heard from the clinical experts that the 6MWT was not used to assess mobility in clinical practice in England and was not persuaded that 6MWT distance was an appropriate outcome measure for all people with paediatric-onset hypophosphatasia (especially babies and young children). The committee was uncertain about how credible the company's minimal clinically important difference in 6MWT distance was for paediatric-onset hypophosphatasia, given that it was based on people with Duchenne muscular dystrophy. The committee considered that there were important differences in the natural history between juvenile-onset hypophosphatasia and Duchenne muscular dystrophy (for example, life expectancy). However, the committee acknowledged that the company's clinical trial data suggested that the minimal clinically important difference was similar between the conditions, and noted that changing the threshold for a minimal clinically important difference in the economic model had a small effect on the results. The committee concluded that it would have preferred the company's model structure to capture all symptoms of hypophosphatasia, but accepted that using 6MWT distance to define health states was reasonable given the lack of evidence allowing for alternative structures.

5.22 The committee discussed the use of the ordered probit regression model to estimate the transition probabilities. The committee noted that the company used separate probit models for estimating transitions for asfotase alfa and for best supportive care and the ERG preferred a single probit model controlled for treatment effect. The committee highlighted that using either approach estimated similar results in the company's economic model. It understood from the company that each analysis provided nearly identical Markov traces. The committee concluded that it preferred the ERG's approach given the limited number of observations for best supportive care, but was prepared to accept

the company's results in its decision-making because the results were similar for the 2 different approaches.

- 5.23 The committee discussed the most appropriate method for modelling overall survival and the need for invasive ventilation. The committee noted that, in the company's base case, the risk of mortality and the need for invasive ventilation for people with perinatal- and infantile-onset hypophosphatasia were not included. The committee recalled its earlier discussions around the natural history data and agreed that any potential for bias when comparing the effect of asfotase alfa with best supportive care should also be addressed in the economic modelling when possible (for example, year of diagnosis and changes in practice over time, and differences between baseline populations that influence prognosis; see [section 5.5](#)). The committee was aware that the ERG's exploratory analysis had attempted to address the potential bias associated with the natural history data. The committee noted that the estimate of incremental life years reduced by 1 life year when using survival data from people in the historical control group who were diagnosed in 2000 or later compared with using survival data from all historical controls. The committee concluded that using natural history data that attempted to adjust for the potential biases was appropriate in the economic modelling.
- 5.24 The committee noted that the company had initially assumed a reduction in the price of asfotase alfa after 10 years because of a loss of data exclusivity. It understood the company's justification for this approach, but considered that there was no robust basis for making this assumption and that the size of the reduction was arbitrary. The committee stated that it had not previously considered price reductions resulting from the potential introduction of generics or biosimilars because this 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 further noted that NICE's [guide to the methods of technology appraisal](#) (2013) states that a reduced price should only be used when there is a nationally available price reduction. The committee concluded the price reduction after 10 years was inappropriate and recognised that this assumption had been removed from subsequent analyses.
- 5.25 The committee discussed other costs and healthcare resources used in the company's model. The committee noted the evidence submission from NHS

England and the views of the clinical experts that suggested babies with paediatric-onset hypophosphatasia would need several months of intensive care and invasive ventilation. The committee understood from the ERG that the company's reporting of resource use data did not enable the ERG to identify how each estimate was obtained. However, the ERG noted that the face validity of the company's estimates seemed acceptable. The committee concluded that the costs of intensive care and invasive ventilation in the company's model were reasonable estimates, but they were associated with uncertainty because the company's resource use data were not fully transparent.

5.26 The committee discussed the utility values used in the company's model. The committee heard from the patient experts that the health-related quality of life of a child with hypophosphatasia can be substantially lower than that of a child without hypophosphatasia of the same age. The committee noted that the company's mean utility value for the most severe 6MWT health state was 0.23, which represented a very low health-related quality of life with the potential to accentuate any benefits of treatment. The committee also acknowledged that the company had not included the health-related quality-of-life benefits for carers of people with the condition and that, if included, they were likely to increase the quality-adjusted life year (QALY) gain for asfotase alfa compared with best supportive care. The committee concluded that the mean utility values used in the company's model were reasonable estimates for the 6MWT health states.

5.27 The committee discussed the company's scenario in which the baseline age and severity were adjusted to match those of people for whom asfotase alfa would be considered under the proposed managed access arrangement (see [section 4.25](#)). The committee considered that, because the proposed managed access arrangement aimed to identify people with the greatest clinical need, it was logical that the baseline disease severity in the managed access arrangement population would be worse than the whole population. It also considered that it was sensible for the model to attempt to reflect the population that would be treated in clinical practice as closely as possible. However, it noted that there was very limited evidence to support the specific values chosen by the company, so it was unable to conclude whether the results were necessarily more accurate than those from the base case. In particular, it recalled that the age of starting treatment had an impact on the QALY gain (see [section 4.25](#)). However, it noted that the very small number of people currently

having treatment with asfotase alfa meant that any patients starting or stopping treatment would have a large impact on the mean age and, therefore, the results from the model. The committee considered that the revision in baseline age illustrated the underlying uncertainty in the company's model. It concluded that the assumptions in this scenario, although logical, were uncertain.

5.28 The committee discussed the most appropriate discounting rate used for costs and health effects. The committee heard from the company on several occasions that it considered a discounting rate of 1.5% to be most appropriate because of the clinical benefit associated with asfotase alfa treatment and the consistency with discounting rates used in evaluations of eculizumab for atypical haemolytic uraemic syndrome and elosulfase alfa for mucopolysaccharidosis type IVa. The committee understood from the company's sensitivity analyses that the results of the company's cost-consequence model were sensitive to the discounting rate. It was aware that changing the discounting rate from 1.5% to 3.5% resulted in a change in incremental QALYs for asfotase alfa compared with best supportive care from approximately 25 to 14. The committee noted that the incremental costs were also affected when changing the discounting rate in the company's economic model. The committee was aware from NICE's [guide to the methods of technology appraisal](#) (2013) that a non-reference case discounting rate of 1.5% for costs and benefits may be considered by the committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits will be achieved. Further, the committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs. The committee acknowledged that asfotase alfa may restore some people (for example, babies) who would otherwise die or have a very severely impaired life to full or near full health. However, it was not convinced on the balance of the clinical evidence, and the clinical expert and patient expert testimonies, that this was the case for all people with paediatric-onset hypophosphatasia (see sections [5.1](#) and [5.2](#)). Also, the committee agreed that there was considerable uncertainty around whether the treatment effect would be maintained for the person's lifetime. The committee concluded that, on the basis of the evidence presented, it was very uncertain whether the long-term health benefits will be achieved and that it was therefore more appropriate for the company to include a discounting rate of 3.5% in its base-case analysis.

5.29 The committee discussed the results of the company's cost-consequence

model. It noted that in the company's deterministic base case, asfotase alfa was associated with 25.04 incremental QALYs over the lifetime of the model. The total costs for asfotase alfa and incremental costs for asfotase alfa compared with best supportive care are commercial in confidence and cannot be reported here. However, the committee highlighted that there were a number of uncertainties in the economic model (see sections 5.21 and 5.23). The committee stated that the company's probabilistic sensitivity analysis suggested that the results were not very stable, suggesting that there was considerable uncertainty, particularly for the estimation of QALY gains (that is, 18.4 incremental QALYs in the probabilistic sensitivity analysis compared with 25.04 in the corresponding deterministic base-case analysis). It was aware that the company had assumed the treatment effect was maintained for the person's lifetime, which it considered uncertain, and that the ERG was concerned that the company's vignettes did not capture the true variation around the health-related quality of life of patients between the 6MWT health states (see [section 4.39](#)). The committee considered that these 2 factors were likely to affect the size of the estimated QALY gain. The committee concluded that asfotase alfa provided a substantial QALY gain compared with best supportive care, but there was considerable uncertainty around the size of the benefit.

5.30 The committee discussed the results of the company's cost-consequence model when it was presented by the age that treatment began. The incremental costs for asfotase alfa compared with best supportive care are commercial in confidence and cannot be reported here. The committee noted that there was significant variation in the QALY gain associated with asfotase alfa across the different age groups; the size of this variation was smaller when the population baseline characteristics were adjusted to match the managed access arrangement population. The perinatal- and infantile-onset age group had the greatest life year and QALY gain, and that the life year gain stopped and incremental QALYs gradually reduced as the age increased. The committee noted that there was a substantial reduction in incremental QALYs for people who had treatment with asfotase alfa for paediatric-onset hypophosphatasia when they were 18 years and over. The committee recalled that asfotase alfa is life-saving for the perinatal- and infantile-onset age group (see [section 5.5](#)), whereas the older age groups have a near normal life expectancy (see [section 5.2](#)), so the nature of the treatment benefit would be different in these groups. The committee recalled that there was significant uncertainty in the size of the benefits of treatment with asfotase alfa (see [section 5.29](#)), but that there

was comparatively less uncertainty that treatment with asfotase alfa is life-saving for people with perinatal- and infantile-onset hypophosphatasia (see section 5.5). The committee therefore concluded that the benefits of asfotase alfa in people with perinatal- and infantile-onset hypophosphatasia were of a different nature to those in the older groups, and that they were also both the largest and the least uncertain in this population group.

- 5.31 The committee considered the overall value for money provided by asfotase alfa for treating paediatric-onset hypophosphatasia in the context of other highly specialised technologies. It was aware that NHS England has a single budget for specialised services, which includes a budget for high-cost drugs, and therefore considered the value for money in the context of other highly specialised technologies that are funded within that budget. The committee considered the needs of people with paediatric-onset hypophosphatasia and their families compared with the needs of people with other rare diseases and conditions. It then discussed the overall value of asfotase alfa, taking into account both its health benefits (estimated to be between 14 and 25 additional QALYs) and associated costs, in the context of other highly specialised technologies:
- It recalled that NICE's guidance on [eculizumab for treating atypical haemolytic uraemic syndrome](#) stated that eculizumab produced similar incremental QALY gains when compared with standard care (estimated to be 25.22 by the company and 10.14 by the ERG). NICE estimated an annual cost per patient for eculizumab of £211,000 to £340,000. The committee was aware that no patient access scheme had been agreed for eculizumab.
 - It recalled that NICE's guidance on [elosulfase alfa for treating mucopolysaccharidosis type IVa](#) stated that elosulfase alfa compared with standard care produced incremental QALY gains that were estimated to be 18.18 by the company and 10.03 by the ERG. NICE estimated that the average cost per year for elosulfase alfa was £394,680 per patient (based on the recommended dosage and an average body weight of 25.3 kg). However, the price paid by the NHS is lower than this because of a patient access scheme that provides elosulfase alfa with a confidential discount, and further confidential commercial arrangements between the company and NHS England in a managed access agreement.
- 5.32 The committee noted that the confidential commercial terms for asfotase alfa substantially reduced the cost to the NHS for this treatment. It also noted that these terms, alongside the starting and stopping criteria in the managed access

arrangement, reduced the risks to the NHS and managed the uncertainties associated with this technology. The committee recognised that asfotase alfa was still a high-cost drug, but that it provides substantial benefits. The committee concluded that, with the confidential commercial terms and within the conditions of the managed access arrangement, asfotase alfa provided appropriate value for money.

- 5.33 The committee considered whether it should take into account the consequences of the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism, when evaluating asfotase alfa. The committee noted NICE's position statement about this, and accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this evaluation of asfotase alfa. It therefore concluded that the PPRS payment mechanism was irrelevant in considering the value for money offered by asfotase alfa.
- 5.34 The committee discussed the company's comment in its response to consultation, which disagreed with the committee's conclusion that the PPRS payment mechanism was irrelevant in considering the value for money offered by asfotase alfa (see section 5.33). The committee understood that the company considered that this did not reflect that the 'net cost of asfotase alfa after PPRS payments was lower than the cost of asfotase alfa being considered by the committee'. The committee did not accept that a predicted rebate could function as the guarantee necessary for a 'nationally available price reduction', as envisaged in the guide to methods of technology appraisal 2013. This is unlike patient access schemes and nationally available price reductions resulting from activities of the Commercial Medicines Unit, which are supported by the Department of Health. The committee was aware that, although the PPRS rebate will be paid to the Department of Health, the 2014 agreement did not specify that the money would be re-invested in the NHS. Furthermore, it noted that future rebates were based on forecasts and would be retrospectively adjusted. It therefore considered that it was far from certain that a PPRS 2014 rebate could be accurately quantified and would result in a price reduction that was relevant when considering the value for money offered by a technology. The committee further noted that any rebate from the PPRS agreement

attributable directly to asfotase alfa would not be applied directly to invoices generated by people providing asfotase alfa for treating paediatric-onset hypophosphatasia. This is unlike simple discounts from patient access schemes that have been approved by the Department of Health, and medicines procured for use in secondary care through contracts negotiated by the NHS Commercial Medicines Unit. It therefore considered it would be unlikely that savings would be gained directly in the NHS by local commissioners. The committee concluded that the PPRS 2014 payment mechanism could not be considered a nationally available price reduction. It therefore endorsed NICE's position statement on the PPRS scheme and concluded that the PPRS payment mechanism was not applicable to the consideration of the value for money of asfotase alfa.

Impact of the technology beyond direct health benefits and on the delivery of the specialised service

- 5.35 The committee considered the potential wider societal benefits of asfotase alfa treatment proposed by the company and the patient experts. It understood from the patient experts that because asfotase alfa improves the general health and functioning of people with paediatric-onset hypophosphatasia, it would enable children with the condition to be educated at school. For adults with the condition and carers of people with the condition, it would enable them to work or at least work for longer. The committee also appreciated that asfotase alfa may reduce: the need to move house to be closer to specialist treatment centres; the need for home adaptations (for example, installation of oxygen or changes to help mobility); and the substantial expenses associated with frequent travel to hospital appointments. The committee was also aware that the company's estimates for cost savings used a human capital approach and that the estimates for cost savings would have been lower if a friction cost approach had been used. On balance, the committee agreed that there would be cost savings and benefits with asfotase alfa incurred outside the NHS and personal and social services, but it did not consider them to be qualitatively greater than those provided by other similar highly specialised technologies.
- 5.36 The committee discussed the impact of asfotase alfa on the delivery of specialised services. It noted the submission received from NHS England indicating that it did not envisage the need for substantial training or education of staff, and that administration of asfotase alfa was straightforward. The committee understood from the company that no additional infrastructure

would be needed at the 3 specialist centres currently treating hypophosphatasia in England (Birmingham, Manchester and Sheffield). The committee noted that NHS England had highlighted that several months of intensive care and invasive ventilation may be needed for babies until their condition stabilises. It heard from the clinical experts that, because the survival of babies was expected to improve if asfotase alfa is made available in the NHS, they hoped the current capacity of paediatric intensive care units could cope with this increase in demand, but that this was uncertain and would need to be monitored. The committee further heard that there were major concerns about the capacity of paediatric intensive care units in England in general (not specific to hypophosphatasia) but agreed that this was beyond the remit of the current evaluation. The committee recalled its consideration that the managed access arrangement could impose an additional burden on centres delivering asfotase alfa and that it had been reassured that the centres were well set up to manage the requirements of the arrangement. The committee concluded that, based on the company's estimates for the number of people in England likely to have asfotase alfa and reassurance from the clinical experts, it was satisfied that no major changes in staffing and infrastructure would be needed overall at the 3 specialist centres in England currently treating hypophosphatasia if asfotase alfa was made available.

Conclusion

- 5.37 The committee appreciated that paediatric-onset hypophosphatasia is a rare, serious, life-threatening and debilitating condition that has severe effects on the lives of people with the condition, as well as their families and carers, for which there are few treatment options and there is an important unmet need. After considering all available evidence, and the opinions of the clinical and patient experts, the committee recognised that asfotase alfa represents an important development in the treatment of paediatric-onset hypophosphatasia. The committee agreed that the results of the trials generally suggested that asfotase alfa was associated with clinically meaningful improvements across a range of outcomes when compared with either pre-treatment measurements or with natural history data from patients who had received best supportive care. It acknowledged that asfotase alfa improved survival in babies with perinatal- and infantile-onset hypophosphatasia, and was associated with a considerable QALY gain. However, the committee believed that, given the designs of the trials and several issues with the natural history data, there was considerable uncertainty

around the robustness of the results and the precise size of the benefit. The committee was also concerned that the natural history of paediatric-onset hypophosphatasia in children and adults was not entirely clear (including for people who survive the early years of perinatal- and infantile-onset hypophosphatasia). It considered that the potential benefit with asfotase alfa was not the same for all people with juvenile-onset hypophosphatasia. The committee recognised that the starting and stopping criteria in the managed access arrangement were developed and refined with input from clinical and patient experts and NHS England, to identify people with the greatest clinical need for treatment. It considered that the refined criteria were appropriate. The committee also considered the confidential commercial terms under which asfotase alfa would be made available, and noted that they substantially reduced the costs and risks to the NHS associated with this technology. Although there remained important uncertainties in the cost-consequence model results, the committee considered that asfotase alfa provides major benefits for some people with paediatric-onset hypophosphatasia – particularly those with perinatal- and infantile-onset disease, in whom the benefits are highest and least uncertain. The committee concluded that, although asfotase alfa was a high-cost drug, the costs were manageable in the context of a highly specialised service and it provided appropriate value for money. It further concluded that asfotase alfa should be recommended as an option for treating paediatric-onset hypophosphatasia, for the duration of and within the conditions set out in the managed access arrangement, when the company provides asfotase alfa with the confidential commercial terms agreed with NHS England.

Summary of evaluation committee's key conclusions

HST6	Evaluation title: Asfotase alfa for treating paediatric-onset hypophosphatasia	Section
Key conclusion		

<p>Asfotase alfa is recommended as an option for treating paediatric-onset hypophosphatasia only:</p> <ul style="list-style-type: none"> • for people who meet the criteria for treatment within the managed access arrangement (see section 4.18), and • for the duration of this arrangement and in line with the other conditions it specifies, and • when the company provides asfotase alfa with the confidential commercial terms agreed with NHS England. <p>Paediatric-onset hypophosphatasia is a rare, serious, life-threatening and debilitating condition, for which there is an important unmet need. Asfotase alfa is an important development, which provides significant benefits – it is life-saving for people with perinatal- and infantile-onset disease, and is associated with a considerable quality-adjusted life year (QALY) gain. However, there was considerable uncertainty around the robustness of the results and the precise size of the benefit.</p> <p>The starting and stopping criteria in the managed access arrangement were developed to identify people with the greatest clinical need for treatment; the committee considered that the refined criteria were appropriate.</p> <p>The confidential commercial terms substantially reduced the costs and risks to the NHS associated with this technology. Although there remained uncertainties in the economic model results, the committee considered that asfotase alfa provides major benefits – particularly for people with perinatal- and infantile-onset disease, in whom the benefits are highest and least uncertain. The committee concluded that, although asfotase alfa was a high-cost drug, the costs were manageable in the context of a highly specialised service and it provided appropriate value for money.</p>	<p>1.1, 5.37</p>
<p>Current practice</p>	

Nature of the condition, including availability of other treatment options	<p>Paediatric-onset hypophosphatasia is a rare, serious, life-threatening and debilitating condition that severely affects the quality of life of people with the condition, and their families. The signs and symptoms vary widely and can appear any time from birth until adulthood.</p> <p>The committee appreciated that mortality was extremely high in perinatal- and infantile-onset hypophosphatasia.</p> <p>The natural history of paediatric-onset hypophosphatasia was well-defined for the early years of perinatal- or infantile-onset disease, but was not entirely clear for juvenile-onset disease.</p> <p>The committee concluded that a treatment that would reduce mortality and pain would be highly valued because there are currently no treatments available that specifically prevent or delay the progression of hypophosphatasia.</p>	5.1–5.3
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	<p>The committee acknowledged that asfotase alfa offers a lifeline for babies with paediatric-onset hypophosphatasia, who would otherwise die. The committee heard from the clinical experts that, because asfotase alfa was the first therapy that specifically targets the underlying cause of hypophosphatasia, they considered it to be a step change in the management of paediatric-onset hypophosphatasia.</p>	5.4
Adverse reactions	<p>The company presented adverse event data for people receiving asfotase alfa. Most adverse events were considered unrelated to asfotase alfa treatment and were of mild intensity.</p>	4.17
Clinical evidence		

Availability, nature and quality of evidence	The company identified 4 open-label phase II studies of asfotase alfa and 3 retrospective non-interventional studies.	4.3, 4.4
	Most of the company's clinical trial evidence did not include a concurrent control group. The committee agreed that it was reasonable in the circumstances for the company to compare with natural history data.	5.6
Uncertainties generated by the evidence	Given the heterogeneous nature of the condition and the trial designs used, the available clinical evidence did not provide either a robust estimate of the size of the benefit or a strong indication of the likely variation in the treatment effect.	5.6, 5.10, 5.28
	The committee agreed that there was considerable uncertainty around whether the treatment effect would be maintained for the person's lifetime. The committee heard from the clinical experts that there remained uncertainty about how long treatment was likely to be appropriate after stabilising the condition in clinical practice.	
Impact of the technology	Asfotase alfa improved the probability of survival in perinatal- and infantile-onset hypophosphatasia compared with best supportive care, and the trials generally suggested that treatment was associated with improvements compared with baseline across several outcomes for people with paediatric-onset hypophosphatasia. However, the available evidence did not provide a robust estimate of the size of the benefit – asfotase alfa provided a substantial QALY gain but there was considerable uncertainty around this benefit. The benefits of asfotase alfa were different in nature between different age groups, and the benefits were smaller and more uncertain in older age groups.	5.5–5.7, 5.29, 5.30
Cost evidence		
Availability and nature of evidence	The committee discussed the company's cost–consequence model and budget impact analysis.	5.16–5.34

Uncertainties around and plausibility of assumptions and inputs in the economic model and budget impact analysis	The number of children and adults with paediatric-onset hypophosphatasia who would be treated in the future was uncertain.	5.17
	Assuming 100% adherence was more appropriate for the budget impact analysis.	5.18
	It would have been preferable to capture all symptoms of hypophosphatasia in the model, but using the 6 minute walk test (6MWT) distance to define health states was reasonable.	5.21
	Using natural history data that attempted to adjust for the potential biases was appropriate in the economic modelling.	5.23
	A 30% price reduction after 10 years to account for loss of exclusivity is inappropriate.	5.24
	Costs of intensive care were reasonable, but were uncertain because the resource use data were not transparent.	5.25
	Revisions made to baseline age and severity for people with juvenile-onset disease to account for the managed access arrangement were logical, but uncertain.	5.27
	The most appropriate discounting rate was 3.5%.	5.28
	Probabilistic sensitivity analysis suggested that the results of the cost-consequence analysis were not very stable and were therefore associated with considerable uncertainty.	5.29

<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The committee understood that the health-related quality of life of a child with hypophosphatasia can be substantially lower than that of a child without hypophosphatasia. The utility values in the company's model were reasonable estimates.</p> <p>The committee acknowledged that the company had not included the health-related quality-of-life benefits for carers of people with the condition and that, if included, they were likely to increase the QALY gain for asfotase alfa compared with best supportive care.</p>	5.26
<p>Cost to the NHS and PSS</p>	<p>The committee considered the total cost of asfotase alfa for the whole managed access arrangement population and for the different forms of hypophosphatasia (that is, perinatal and infantile onset, children with juvenile onset and adults with juvenile onset), taking into account the confidential commercial terms.</p> <p>The commercial terms and the refined managed access arrangement reduced the cost to the NHS and reduced the financial risk, compared with previous proposals.</p> <p>On balance, although asfotase alfa was still a very high-cost technology, with the agreed commercial terms the total cost to the NHS was acceptable and manageable in the context of a highly specialised service.</p>	5.19, 5.20
<p>Value for money</p>	<p>Asfotase alfa provided a substantial QALY gain, but there was considerable uncertainty around the size of the benefit.</p>	5.29

	<p>The benefits in people with perinatal- and infantile-onset hypophosphatasia were of a different nature to those in the older groups, and were also the largest and the least uncertain in this group.</p>	5.30
	<p>The committee noted that the confidential commercial terms substantially reduced the cost to the NHS for asfotase alfa, and reduced the risks to the NHS and managed the uncertainties. Asfotase alfa was still a high-cost drug, but provided substantial benefits. The committee concluded that, with the confidential commercial terms and within the conditions of the managed access arrangement, asfotase alfa provided appropriate value for money.</p>	5.32
Impact beyond direct health benefits and on the delivery of the specialised service	<p>The committee agreed that there would be cost savings and benefits with asfotase alfa incurred outside the NHS and personal and social services, but it did not consider them to be qualitatively greater than those provided by other similar highly specialised technologies.</p> <p>The committee considered that the managed access arrangement could impose an additional burden on centres delivering asfotase alfa, but was reassured that the centres were well set up to manage the requirements.</p> <p>Overall, no major changes in staffing and infrastructure would be needed at the 3 specialist centres in England currently treating hypophosphatasia if asfotase alfa were made available.</p>	5.35, 5.36
Additional factors taken into account		

Access schemes	<p>The committee considered the confidential commercial terms agreed with NHS England.</p> <p>The committee also discussed the proposed managed access arrangement. It considered that the finalised starting and stopping criteria were appropriate. It welcomed the inclusion of the national expert committee in the decision-making process, and emphasised the value of the multidisciplinary approach. The committee emphasised the importance of robust governance procedures. The committee concluded that the data collection was likely to provide valuable evidence to support a review of the guidance. It was reassured that the managed access arrangement would not impose an undue burden on people with hypophosphatasia or the NHS.</p>	3.4, 5.9–5.15, 5.19 5.20, 5.31, 5.32
Equalities considerations and social value judgements	No equality issues were raised during the evaluation.	–

6 Implementation

- 6.1 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.
- 6.2 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 evaluation determination.
- 6.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has 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.
- 6.4 The company has proposed that asfotase alfa will be available to the NHS under commercial terms agreed with NHS England. The nature of these terms are commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the commercial terms should be directed to GlobalGovernmentAffairs@Alexion.com.

7 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 to be appraised. If it is considered that there is a conflict of interest, the member is excluded from participating further in that appraisal.

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.

NICE project team

Each highly specialised technology evaluation is assigned to a team consisting of 1 or more technical personnel and project managers, and the Associate Director for the Highly Specialised Technologies Programme.

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Accreditation

