The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using asfotase alfa in the context of national commissioning by NHS England. The highly specialised technologies evaluation committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts, patient experts and NHS England.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the committee. NICE invites comments from the consultees and commentators for this evaluation and the public. This document should be read along with the evidence base (the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance on the use of asfotase alfa in the context of national commissioning by NHS England?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final evaluation determination.
- Subject to any appeal by consultees, the final evaluation determination may be used as the basis for NICE's guidance on using asfotase alfa in the context of national commissioning by NHS England.

For further details, see the Interim Process and Methods of the Highly Specialised Technologies Programme.

The key dates for this evaluation are:

Closing date for comments: 13 October 2016

Fourth evaluation committee meeting: TBC
1 Recommendations

1.1 Asfotase alfa is recommended as an option for treating the bone manifestations of hypophosphatasia, only:

- in people with perinatal- and infantile-onset disease and
- for the duration of, and within the conditions set out in, the proposed managed access agreement for asfotase alfa and
- when the company provides asfotase alfa with the proposed annual per-patient cost cap and
- when the company provides opportunities to reduce the short-term cost of asfotase alfa to the NHS.

1.2 Asfotase alfa is not recommended for treating the bone manifestations of hypophosphatasia in children with juvenile-onset disease. The committee considered that asfotase alfa could provide important clinical benefits for some children with juvenile-onset hypophosphatasia. However, the cost of asfotase alfa is very high, and there are significant uncertainties about its long-term benefits, who would benefit the most from treatment, and the number of people in this patient group who might be eligible for treatment. The committee considered that asfotase alfa had the potential to provide appropriate value for this group, but not under the conditions presented in the proposed managed access agreement and cost cap.

1.3 Asfotase alfa is not recommended for treating the bone manifestations of hypophosphatasia in adults with juvenile-onset disease.

1.4 This guidance is not intended to affect the position of patients whose treatment with asfotase alfa was started within the NHS before this guidance was published. Treatment of those patients may continue
without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

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
- odonto-hypophosphatasia (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. Babies who present with hypophosphatasia in the first 6 months of life 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 with an annual per-patient cost cap. The level of the cap is commercial in confidence.

4 Evidence submissions

The evaluation committee (section 8) considered evidence submitted by Alexion, a review of this submission by the evidence review group 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 receiving 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 receiving 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 receiving 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 hypophosphatasias. The mean EQ-5D score for children receiving asfotase alfa was 0.76 (n=2) and 0.43 in children who did not receive 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 receiving 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).

Company’s managed access agreement

4.18 The company proposed a managed access agreement, which it revised after advice from NICE, and with input from patient groups and clinical
experts. The revised agreement was proposed to last 5 years, and defined criteria for starting and stopping asfotase alfa treatment, and monitoring and data collection requirements:

- **Starting criteria**: The managed access agreement specified that all people with perinatal- and infantile-onset hypophosphatasia, regardless of current age, would start treatment with asfotase alfa. It also specified that asfotase alfa would also be considered for children (aged 1–17 years) with juvenile-onset disease, and intractable musculoskeletal pain or restriction of mobility, and for adults (18 years and over) with juvenile-onset disease and 2 of the following: current fractures or a history of fractures characteristic of hypophosphatasia, intractable musculoskeletal pain and restriction of mobility.

- **Stopping criteria**: The managed access agreement specified a minimum treatment period of 1 year at a stable dose for all patients, and that all babies under 1 year with respiratory problems would continue treatment for the duration of the agreement. It specified that treatment response would be assessed every year at a specialist centre. In children with juvenile-onset disease, it specified that treatment would stop if 3 of the 4 stopping criteria were met: loss of height or growth impairment, no improvement in physical function, fall in Bleck mobility score and no reduction in pain. In adults with juvenile-onset disease, it specified that treatment would stop if 1 of the same criteria were met. After stopping, it specified that disease progression would be assessed every 6 months, and treatment restarted immediately if the disease worsened.

- **Monitoring and data collection**: The managed access agreement specified that data would be collected from everyone who received asfotase alfa within the managed access agreement, and that the data would normally be recorded in the company’s global hypophosphatasia registry. This registry collects data on the natural history and epidemiology of hypophosphatasia, the burden of disease (including clinical outcomes and quality of life), and the safety and effectiveness
of asfotase alfa. The company stated that NHS England would be provided with relevant data extracts from the 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 discount rate of 3.5% per year was presented in a scenario analysis.

4.20 Observations of the 6MWT were available from the trials for 28 people with either infantile- or juvenile-onset hypophosphatasia who received 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 receiving asfotase alfa and 34 observed transitions for people receiving 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 receiving asfotase alfa and
- decreased by 13.6 m and 3.91 percentage points in per cent predicted in people receiving 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 proposed annual per-patient cost cap, using the recommended dosage in the summary of product characteristics. The company assumed that the list price for asfotase alfa reduced by 30% after 10 years because of a loss of data exclusivity. 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

<table>
<thead>
<tr>
<th>Health state</th>
<th>Annual cost</th>
<th>Utility value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity level I</td>
<td>£1,399</td>
<td>0.86</td>
</tr>
<tr>
<td>Severity level II</td>
<td>£3,976</td>
<td>0.67</td>
</tr>
<tr>
<td>Severity level III</td>
<td>£5,846</td>
<td>0.54</td>
</tr>
<tr>
<td>Severity level IV</td>
<td>£14,358</td>
<td>0.23</td>
</tr>
<tr>
<td>Scenario analysis (when starting age is below 5 years)</td>
<td>£399,467</td>
<td>−0.33</td>
</tr>
</tbody>
</table>

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 and therefore cannot be reported here. In the company’s base case (discount 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).
4.24 The company explored parameter and structural uncertainty in its economic model in 1-way sensitivity analyses and scenario analyses. The 1-way sensitivity analysis suggested that the results were most sensitive to the discount rate used for costs and health effects, and changes to the utility values. The company presented a scenario analysis that varied the threshold defining the difference in 6MWT distance between each severity level state from 8.9% to 26.7% from a base-case value of 17.8% (twice the minimal clinically important difference in Duchenne muscular dystrophy). This reduced the incremental QALYs in both scenarios from 25.0 in the base case to 17.9 and 19.6 respectively, but had little effect on the incremental cost.

4.25 The company presented the results of its probabilistic sensitivity analysis of asfotase alfa compared with best supportive care based on 500 simulations. Incremental costs are commercial in confidence and cannot be presented here. Asfotase alfa treatment produced an additional 18.4 QALYs compared with best supportive care (34.2 total QALYs and 15.8 total QALYs respectively).

4.26 The company presented the results of its cost–consequence analysis for subgroups based on the age at which treatment began. Incremental costs are commercial in confidence and cannot be presented here. Asfotase alfa treatment produced an additional 31.7 QALYs for the perinatal- and infantile-onset group, and an additional 5.1–29.0 QALYs for people with juvenile-onset disease (see table 2). 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, from 19.7 QALYs in the 18–20 years age group to 2.5 QALYs in the 61–65 years age group.

**Table 2 Results of the company’s cost–consequence analysis grouped by the age at which treatment began**

<table>
<thead>
<tr>
<th></th>
<th>Perinatal-</th>
<th>Juvenile-onset</th>
</tr>
</thead>
</table>

National Institute for Health and Care Excellence

Evaluation consultation document – Asfotase alfa for treating paediatric-onset hypophosphatasia

Issue date: September 2016
### Cost to the NHS and personal social services

The company also presented the results of its cost–consequence analysis for the population who would be considered for treatment within the proposed managed access agreement. Incremental costs are commercial in confidence and cannot be presented here. In the managed access agreement population, asfotase alfa treatment produced a weighted-average QALY gain of 27.5 QALYs for people under 18 years and a weighted-average QALY gain of 5.1 QALYs for people 18 years and over.

<table>
<thead>
<tr>
<th>Incremental QALYs</th>
<th>0–4 years</th>
<th>5–11 years</th>
<th>12–17 years</th>
<th>18 years and over</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>31.70</td>
<td>28.99</td>
<td>24.87</td>
<td>22.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.07</td>
</tr>
</tbody>
</table>

Abbreviation: QALY, quality-adjusted life year.

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 the German Beck et al. (2003) study 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 presented the results of a budget impact analysis over 5 years (see table 3). The company 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, and taking into account the proposed cost cap. The company assumed an 80% rate of adherence, with a 100% rate of adherence explored in a scenario analysis. 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. The company estimated the number of people for whom treatment would be considered within the proposed managed access agreement, taking into account published data from the US (Whyte et al., 2015) and surveys of expert centres in the UK. The company presented estimates for the total number of people receiving asfotase alfa within the proposed managed access agreement. These estimates are commercial in confidence and cannot be reported here; despite multiple requests from NICE, the company refused to make its estimates of the number of people likely to receive asfotase alfa publicly available. The number of deaths avoided over 5 years with asfotase alfa treatment was 38.5.

### Table 3 Results of the company’s budget impact analysis

<table>
<thead>
<tr>
<th></th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Budget impact at 80% adherence (£ millions)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA and BSC</td>
<td>5.09</td>
<td>6.77</td>
<td>7.85</td>
<td>8.95</td>
<td>10.06</td>
</tr>
<tr>
<td>Without AA</td>
<td>0.49</td>
<td>0.49</td>
<td>0.50</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td>Net budget impact</td>
<td>4.60</td>
<td>6.27</td>
<td>7.35</td>
<td>8.45</td>
<td>9.56</td>
</tr>
<tr>
<td><strong>Budget impact at 100% adherence (£ millions)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA and BSC</td>
<td>5.42</td>
<td>7.24</td>
<td>8.39</td>
<td>9.56</td>
<td>10.74</td>
</tr>
<tr>
<td>Without AA</td>
<td>0.49</td>
<td>0.49</td>
<td>0.50</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td>Net budget impact</td>
<td>4.93</td>
<td>6.75</td>
<td>7.90</td>
<td>9.06</td>
<td>10.24</td>
</tr>
</tbody>
</table>

Abbreviations: AA, asfotase alfa; BSC, best supportive care.

### Evidence review group review

#### Clinical evidence

4.30 The ERG did not believe any relevant studies were missed by the company’s searches.
4.31 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, 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.

4.32 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 receiving 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.

4.33 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.

4.34 The ERG agreed that people receiving 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.

4.35 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**

4.36 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.

4.37 The ERG preferred that the costs and health effects were discounted at an annual rate of 3.5% rather than the 1.5% in the company’s base case. It explained that the evidence was not sufficiently clear 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 that the long-term effects of treatment were uncertain. The ERG acknowledged that the company’s economic model indicated that more people would be in the least severe health states. However, the ERG was uncertain as to what extent this could be considered ‘full health’ and whether the
treatment effect would be maintained for their lifetime. Therefore, the ERG concluded that a discount rate of 1.5% was not appropriate.

4.38 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 receiving 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).

4.39 The ERG noted that it was not clear how the baseline age and severity levels were derived or whether they reflected a UK paediatric-onset hypophosphatasia population.

4.40 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.

4.41 The ERG considered that reducing the price for asfotase alfa after 10 years because of a loss of data exclusivity was not appropriate. The ERG also noted that the size of the discount was not reasonably justified by the company. The ERG noted that the company did not include costs associated with personal social services.

4.42 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.

4.43 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 4.38)
- 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%.

Total costs and incremental costs for asfotase alfa compared with best supportive care for all analyses are commercial in confidence and therefore cannot be reported here. At a discount rate of 3.5%, the ERG estimated that asfotase alfa was expected to 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).

4.44 The ERG presented the results of its exploratory cost–consequence analysis for asfotase alfa compared with best supportive care in subgroups based on the age at which treatment began. Incremental costs are commercial in confidence and cannot be presented here. Asfotase alfa treatment produced an additional 15.6 QALYs for the perinatal- and infantile-onset group, and 9.8–14.7 QALYs for people with juvenile-onset disease (see table 4).

### Table 4 Results of the ERG’s exploratory cost–consequence analysis grouped by the age at which treatment began

<table>
<thead>
<tr>
<th>Perinatal- and infantile-onset</th>
<th>Juvenile-onset</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–4 years</td>
</tr>
<tr>
<td>Incremental QALYs</td>
<td>15.6</td>
</tr>
</tbody>
</table>

Abbreviation: QALY, quality-adjusted life year.

4.45 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 and therefore cannot be reported here. At a discount 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**

4.46 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 discount 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 to be reasonable. The ERG estimated the number of deaths avoided over 5 years with asfotase alfa treatment was 21.4.

4.47 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 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 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 serious, life-threatening and debilitating condition.

5.2 The committee discussed the natural history of paediatric-onset hypophosphatasia. The committee 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. 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. 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.

5.5 The committee discussed the results for overall survival in perinatal- and infantile-onset hypophosphatasia. The committee 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 was still likely to be higher for people receiving asfotase alfa compared with people not receiving asfotase alfa. The committee 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.

5.9 The committee discussed how asfotase alfa would potentially be used in babies with perinatal- and infantile-onset hypophosphatasia, and considered the criteria in the company’s proposed managed access agreement for this group. The committee heard from the clinical experts that, in principle, the decision to treat with asfotase alfa could be based on clinical judgement and would depend on the overall clinical picture. However, the clinical experts agreed that, if available, they would give asfotase alfa to all babies with perinatal- and infantile-onset hypophosphatasia straight away. The committee noted that the managed access agreement proposed that, in babies, all perinatal- and infantile-onset hypophosphatasia should be treated with asfotase alfa, and accepted the clinical experts’ view that these patients would benefit from treatment. The committee also noted the company proposed that, in all babies, treatment should continue for the duration of the managed access agreement. It was aware that asfotase alfa has a marketing authorisation for long-term treatment in all of these patients (irrespective of age at diagnosis or extent of bone manifestations). It 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). However, the committee heard from the clinical experts that there was considerable uncertainty about how long treatment was likely to be appropriate after stabilising the condition in clinical practice. The committee concluded that, based on current evidence, the criteria for starting treatment in babies with perinatal- or infantile-onset hypophosphatasia in the proposed managed access agreement were appropriate. However, it was not able to define a treatment continuation rule for asfotase alfa in this group after the condition has stabilised.
5.10 The committee discussed how asfotase alfa would potentially be used in children and adults with juvenile-onset hypophosphatasia, and considered the aspects of the proposed managed access agreement that relate to this population. The committee was aware that juvenile-onset hypophosphatasia had a variable overall clinical picture and that some children were functioning normally. It heard from the clinical experts that the decision to start or continue 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). Some clinicians would not treat hypophosphatasia in all children and adults without significant morbidity, and the committee further heard from the clinical experts that intermittent treatment would likely be needed for this group. 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 considered the criteria for starting and stopping treatment for people with juvenile-onset hypophosphatasia that were put forward by the company in its managed access agreement (see section 4.18). The committee was aware that the criteria aimed to identify patients with the greatest clinical need, and heard that the criteria had been developed with input from clinical and patient experts. However, the committee recalled evidence that symptoms were highly variable among people with juvenile-onset hypophosphatasia (see section 5.2). It considered that the criteria were broad and not based on objective measures, and so would not adequately identify the group of
people who would benefit most from treatment with asfotase alfa. The committee therefore considered that the proposed managed access agreement did not sufficiently define the population with the greatest clinical need. The committee concluded that the treatment need for children and adults with juvenile-onset hypophosphatasia varied, so the proposed criteria for starting and stopping treatment with asfotase alfa in the managed access agreement were insufficient for identifying the people who would most benefit from asfotase alfa.

5.11 The committee discussed the proposed data collection methods presented within the managed access agreement. The committee considered that the proposed methods lacked detail, and that no formal analysis plan was submitted. The committee was aware that the company proposed to combine the data collection for the managed access agreement with the global hypophosphatasia registry that formed as part of the company’s regulatory commitments. The committee expressed concern that these 2 processes were designed for different purposes. The committee explored the measures of quality of life that were included in the data collection proposal, and was concerned that they would not fully capture the quality of life and experiences of people with hypophosphatasia. The committee considered that the proposed data collection was unlikely to gather sufficient evidence during the course of the managed access agreement to adequately inform a review of the guidance at the end of this period. The committee would have preferred the company to have submitted a detailed protocol to more fully explore the long-term effects of asfotase alfa treatment. It concluded that the proposed data collection methods presented within the managed access agreement had a number of important limitations.

Cost to the NHS and personal social services

5.12 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 had proposed an annual per-patient cost cap for the acquisition cost of asfotase alfa; the cap is commercial-in-confidence and cannot be reported here. The proposed cost cap would have no effect on the costs of asfotase alfa for younger patients until they reach a certain weight and the committee was aware that this would not occur during the period of the proposed managed access agreement for babies with perinatal- and infantile-onset hypophosphatasia. Therefore the committee concluded that NHS England and the company (Alexion Pharma UK) should further explore opportunities for short-term cost reduction arrangements for this group.

5.13 The committee considered the assumptions in the diagnosis rates within the company’s budget impact model. The committee acknowledged that the company had assumed the rate of diagnosis of paediatric-onset hypophosphatasia would increase following the availability of asfotase alfa. This 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, and consequently how many would be eligible for asfotase alfa treatment. Taking these factors into account the committee concluded that the number of people identified in clinical practice with paediatric-onset hypophosphatasia was likely to rise, and that it was possible that a significant proportion of newly diagnosed people would be those who would not benefit the most from asfotase alfa treatment.
5.14 The committee considered the number of diagnosed patients eligible for treatment in the company’s budget impact analysis, which was considered commercial in confidence by the company (see section 4.29). The committee noted that the company estimated the proportion of children with juvenile-onset hypophosphatasia likely to start treatment by using the midpoint of estimates taken from UK and US clinical practice. The committee recognised that it was difficult to estimate patient numbers reliably, but was still not convinced by the company’s justification for its approach and highlighted the wide range between the 2 estimates. It concluded that the number of children who would receive treatment with asfotase alfa within the proposed managed access agreement was uncertain and may be higher than estimated by the company. In addition, the committee considered the treatment rate for adults with juvenile-onset hypophosphatasia, taking into account the starting and stopping criteria proposed in the managed access agreement (see section 4.18). It recalled that it had considered the number of adults with paediatric-onset hypophosphatasia to be uncertain and likely to rise, and the criteria in the managed access agreement to be broad. The committee concluded that the number of adults with paediatric-onset hypophosphatasia treated with asfotase alfa in the company’s analysis likely to be underestimated.

5.15 The committee recalled that the company estimated that the total number of people with paediatric-onset hypophosphatasia in England was 1.9, 149.4 and 553.5 in people aged 0–1 year, 1–17 years, and 18 years and over respectively (see section 4.28). These estimates do not take into account the number of people who would have asfotase alfa, the proposed managed access agreement or any increases in diagnosis rates. However, the committee highlighted that the numbers of people in the 1–17 years and the 18 years and over groups were considerably larger than the number of children with perinatal- and infantile-onset disease (0–1 year group). The committee was aware that the company did not present a breakdown of the budget impact analysis for these age groups. However, taking into account the number of people in these age...
groups and the increase in the cost of asfotase alfa as people get older, the committee considered that the budget impact of asfotase alfa would be substantially larger in children and adults with juvenile-onset hypophosphatasia than in children with perinatal- and infantile-onset disease, despite the proposed cost cap. The committee further considered that, because the number of children and adults with juvenile-onset disease was underestimated (see section 5.14), the budget impact in these groups would also be larger than the company’s estimate.

5.16 The committee was aware that the company had assumed that adherence to asfotase alfa was 80%, with a scenario that explored 100% adherence. The committee heard from the company that it had based its 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 agreed that the scenarios that assumed 100% adherence provided more plausible estimates for the budget impact of asfotase alfa. The committee concluded that the company’s base-case assumption about adherence resulted in a significant underestimate of the budget impact, and that assuming 100% adherence was more appropriate.

5.17 The committee discussed the overall budget impact of asfotase alfa. It emphasised that the net budget impact estimated by the company (see table 3) was high. It recalled its consideration that, because the number of people with perinatal- and infantile-onset disease was small, the budget impact would be smaller than for the other age groups (see section 5.15). The committee also recalled its inference that there was significant risk that the number of people who were eligible for asfotase alfa treatment in the older onset populations was an underestimate (see section 5.14). The committee concluded that the uncertainty surrounding patient eligibility could result in an unreasonable burden to NHS resources, particularly in
the older age groups, which is not shared by the company in the proposed managed access agreement.

5.18 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. However, it was not convinced that the high cost per patient of asfotase alfa was justified compared with the price paid by the NHS for other treatments for rare conditions. The committee was not persuaded that paediatric-onset hypophosphatasia was any rarer than other conditions for which NICE has evaluated highly specialised technologies, especially given its earlier concerns around increasing patient numbers because of an increase in diagnoses (see section 5.13). The committee then heard from the company that asfotase alfa was priced on the basis that most people receiving treatment in clinical practice would be babies. However, the committee highlighted that there was considerable uncertainty around how long babies would continue to receive treatment in clinical practice, and that the company had not provided criteria that identified people with greatest clinical need for ongoing treatment. The committee was not told of any clinical or safety needs during clinical development that might justify the development costs of asfotase alfa being greater than for other treatments for small populations. Furthermore, the committee was not satisfied that there was an explanation of the relationship between the development costs of asfotase alfa and the price being proposed for the NHS. The committee concluded that it had not been given enough
justification for the high cost per person of asfotase alfa, or for the overall cost of asfotase alfa in terms of what could be expected to be reasonable in the context of a highly specialised service.

**Value for money**

5.19 The committee discussed the company’s model structure for the cost–consequence and budget impact analyses. 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.
5.20 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.

5.21 The committee discussed the population included in the company’s economic model. The committee noted that the company presented its base-case cost–consequence analysis for subgroups based on the age at which treatment began, including groups with perinatal- and infantile-onset hypophosphatasia, children with juvenile-onset hypophosphatasia and adults with juvenile-onset hypophosphatasia. The committee also considered the company’s analyses, which took into account the effect the number of people for whom treatment would be considered would have within the proposed managed access agreement.

5.22 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.

5.23 The committee discussed the cost of asfotase alfa used in the company’s
model. It noted the company had proposed an annual per-patient cost cap
for the acquisition cost of asfotase alfa. The committee also noted that the
company had assumed an arbitrary reduction in the price of asfotase alfa
after 10 years because of a loss of data exclusivity. The committee
understood the company’s justification for this approach, but considered
that there was no robust basis for making this assumption. 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 that the costs
associated with asfotase alfa treatment in the economic modelling had
been underestimated by the company.

5.24 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.

5.25 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.

5.26 The committee discussed the most appropriate discount rate used for costs and health effects. The committee heard from the company on several occasions that it considered a discount rate of 1.5% to be most appropriate because of the clinical benefit associated with asfotase alfa treatment and the consistency with discount 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 discount rate. It was aware that changing the discount 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 discount 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 discount 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, 5.2 and 5.10). The committee agreed that there was considerable uncertainty around whether the treatment effect would be maintained for the person’s lifetime, and that it would have been appropriate for the company to explore a scenario in which the treatment effect diminished over time. 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 discount rate of 3.5% in its base-case analysis.

5.27 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 potential bias in the economic model which may cause the incremental costs for asfotase alfa compared with best supportive care to be underestimated (see sections 5.20 and 5.22). 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 company’s deterministic base-case analysis). It was aware that the company had assumed the treatment effect was maintained for the person’s lifetime, 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 4.38). 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.

5.28 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 perinatal- and infantile-onset age group had the greatest QALY gain, and the incremental QALYs gradually reduced as the age increased. The committee noted that there was a significant reduction in incremental QALYs for people who received treatment with asfotase alfa for paediatric-onset hypophosphatasia when they were 18 years and over. The committee concluded that the benefits of asfotase alfa were largest in people with perinatal- and infantile-onset hypophosphatasia.

5.29 The committee considered the overall value for money provided by asfotase alfa for treating paediatric-onset hypophosphatasia. It was aware that NHS England has a single budget for specialised services of £13 billion, which includes a budget of £156 million for high-cost drugs. 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.

The committee was concerned that the number of patients eligible for treatment with asfotase alfa and the budget impact were likely to be underestimated by the company (see section 5.14). It was not convinced that the criteria for starting, stopping and continuing treatment currently proposed by the company in its managed access agreement would appropriately identify those who had the greatest clinical need. Although the committee had considered the evidence of improved outcomes from clinical trials and the patient testimonies, it remained concerned that the size of the health benefits for asfotase alfa compared with best supportive care was associated with considerable uncertainty. It considered that the benefits of treatment were not great enough to justify its high cost (even with the proposed cost cap). The committee was not convinced that
asfotase alfa represented good value for money for the NHS, for the whole population of people with paediatric-onset hypophosphatasia.

5.30 The committee discussed whether there were any groups of people for whom asfotase alfa could be considered to offer greater value for money to the NHS than the whole population covered by its marketing authorisation. It recalled its considerations that perinatal- and infantile-onset hypophosphatasia were the most severe forms of the disease, and that people with perinatal- and infantile-onset hypophosphatasia could gain considerable benefits from treatment. The committee therefore considered separately populations based on the age of onset: people with perinatal- and infantile-onset disease, children with juvenile-onset disease and adults with juvenile-onset disease.

5.31 The committee considered that the perinatal- and infantile-onset population had the greatest unmet need for asfotase alfa treatment (see section 5.9). Asfotase alfa was associated with a considerable QALY gain in this population, and the committee also noted that the nature of the treatment benefits was different compared with older onset age groups. In particular, the committee noted that asfotase alfa can prevent death at a very young age in this population, and so had the potential to produce a gain of a large number of life years. The committee concluded that the total incremental health benefits associated with asfotase alfa compared with best supportive care in the perinatal- and infantile-onset population were substantial. It also concluded that they were associated with fewer uncertainties and a more manageable budget impact compared with the other populations, and were great enough to justify its high total incremental cost. The committee remained concerned at the very high annual per-patient cost for asfotase alfa, which the proposed cost cap would not substantially reduce during the period of the managed access agreement because of the weight-based dosing of the therapy.

5.32 The committee discussed the value for money of asfotase alfa in children with juvenile-onset hypophosphatasia. The committee noted that
treatment with asfotase alfa would be associated with a significant QALY gain. However, it recalled evidence from clinical experts (section 5.10) that suggested that there is significant variation in treatment need within this population, and that there was significant uncertainty about who would benefit most from asfotase alfa treatment. The committee recalled its assessment of the company’s proposed managed access agreement (section 5.10) and the conclusion that it would be ineffective in identifying the people who would most benefit from asfotase alfa treatment within this highly heterogeneous population. Furthermore, the committee considered that there was significant uncertainty about the number of people in this population for whom treatment would be considered, which could adversely affect the budget impact. The committee was aware that the uncertainty within this population could put a considerable financial burden on the NHS and so lead to a considerable risk that other treatments and services might be displaced by investing in such a high-cost technology. The committee concluded that, because of the uncertainties and potential financial burden, asfotase alfa was unlikely to offer appropriate value for money in children with juvenile-onset hypophosphatasia.

5.33 The committee discussed the value for money of asfotase alfa for treating juvenile-onset hypophosphatasia in adults. The committee noted that the QALY gain within this population was significantly lower compared with the other population groups and the population as a whole. Furthermore the committee recalled that there was concern that the proposed start and stop criteria in the managed access agreement were broad and not based on objective criteria (see section 5.10). The committee noted that this meant the number of people for whom treatment would be considered, and therefore the budget impact, could have been underestimated. The committee noted that the proposed annual per-patient price cap would significantly reduce the costs in this group. Nevertheless, the committee concluded that the costs for asfotase alfa in this population were excessively high relative to the benefits of treatment.
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.

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 5.34). 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**

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.

5.37 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). However, the committee heard from the clinical experts that the specialist centre in Manchester would need additional resources, such as long-term physical and occupational therapy, to provide the same level of support services for treating paediatric-onset hypophosphatasia as Birmingham 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 concluded that, based on the company’s estimates for the number of people in England likely to receive 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 (but with the concerns as noted above).
Conclusion

5.38 The committee discussed the recommendation it could make for asfotase alfa for treating paediatric-onset hypophosphatasia. It appreciated that paediatric-onset hypophosphatasia is a 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. 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 was not convinced that the potential benefit with asfotase alfa was the same for all people with juvenile-onset hypophosphatasia. This was supported by the clinical experts, who stated that they were not certain about how this population would be treated in clinical practice, and that only a minority of the prevalent population would have a clinical need for treatment. The committee was not persuaded that the company’s proposed starting and stopping rules for asfotase alfa would identify those people for whom treatment should be a priority. The committee heard from the clinical experts that any criteria for starting, stopping and continuing treatment should be transparent and based on a
combination of clinical, radiological and biochemical outcomes. The committee considered that asfotase alfa has the potential to provide major benefits for some people with paediatric-onset hypophosphatasia, but not the broad group proposed by the company because of the considerable uncertainty. The committee believed that the company’s budget impact and cost–consequence model substantially underestimated the costs associated with asfotase alfa compared with best supportive care, given the uncertainty around the model structure and several of the company’s assumptions. It concluded that, in the paediatric-onset hypophosphatasia population as a whole, the costs and budget impact associated with asfotase alfa were considerable and were too high in the context of the overall benefits that this treatment would provide. The committee therefore concluded that asfotase alfa should not be recommended for the whole population.

5.39 The committee considered that the need for treatment with asfotase alfa and potential benefits differed substantially depending on the age of onset of symptoms and the age of the person having treatment. It therefore considered separately the possible recommendations it could make for asfotase alfa in people with perinatal- or infantile-onset disease, children with juvenile-onset disease and adults with juvenile-onset disease.

5.40 **Perinatal- or infantile-onset disease:** The committee recognised that people in this population had the most severe forms of the disease and could potentially benefit considerably from treatment. It noted that the cost–consequence analysis showed that there was potential for a high QALY gain in this group, although it came at a very high cost. Nevertheless, this population was associated with the fewest uncertainties and the greatest value for money. The committee was aware that the number of patients in this group, and hence the budget impact, were smaller than in the older populations. It considered that the financial risk to the NHS in this group was likely to be manageable, although it was aware that the proposed cost cap will not substantially reduce the cost of asfotase alfa during the period of the managed access agreement. The
committee therefore recommended that NHS England and the company (Alexion Pharma UK) should further explore opportunities for short-term cost reduction of asfotase alfa for this group. The committee concluded that asfotase alfa should be recommended for people with perinatal- or infantile-onset hypophosphatasia for the duration of the managed access agreement. The committee stated that data gathered as part of the managed access agreement should provide information on how long treatment should continue, and when treatment could be stopped or the dose reduced, to inform a review of the guidance at the end of the 5-year period.

5.41 **Children with juvenile-onset disease:** The committee was aware that this population was clinically very different from the perinatal- and infantile-onset population in terms of the need for treatment and the nature and size of the potential benefits. It also considered that the long-term benefits of asfotase alfa were considerably more uncertain in this population. It highlighted that this is a very heterogeneous group, and considered that the proposed managed access agreement did not identify those with the greatest clinical need. The committee noted the size of this group meant the budget impact of asfotase alfa would be substantially greater than for the perinatal- and infantile-onset group. It was concerned about the affordability of such a large investment, and the health benefits that may be displaced elsewhere in the NHS. Taking into account the clinical benefits of the treatment, alongside the value for money and budget impact, the committee recognised that asfotase alfa had the potential to provide appropriate value. However, it considered that the conditions presented in the proposed managed access agreement and proposed cost cap as they stand were not sufficient to recommend asfotase alfa as an appropriate use of NHS resources.

5.42 **Adults with juvenile-onset disease:** The committee highlighted that the benefits of asfotase alfa in this population were considerably lower than in other groups, but the cost of treatment remained high. It considered that asfotase alfa did not provide value for money in this population. The
committee was also aware of the uncertainties in the size of this population, and that an increase in the population size would substantially increase the financial burden to the NHS. The committee highlighted that the need for treatment with asfotase alfa varied considerably within this group, and considered that the proposed managed access agreement did not identify a specific group for whom the clinical need is greatest or who would benefit the most from asfotase alfa treatment. The committee concluded that it could not recommend asfotase alfa for adults with juvenile-onset hypophosphatasia.

5.43 The committee recognised that, because asfotase alfa was recommended only for children with perinatal- and infantile-onset disease, there were limits on the information that could be obtained through the data collection elements of the proposed managed access agreement. In particular, the committee acknowledged that evidence on the longer-term effectiveness of asfotase alfa in children and adults in UK clinical practice, and the appropriateness of particular starting and stopping criteria in these groups, would not be collected. The committee recalled its consideration that there were important limitations in the proposed data collection, and would have preferred the company to have submitted a detailed protocol to more fully explore the long-term effect of asfotase alfa treatment. However, it noted that evidence collected through other studies, including the global hypophosphatasia registry, was likely to be informative for reviewing the guidance when available.

**Summary of evaluation committee’s key conclusions**

<table>
<thead>
<tr>
<th>Key conclusion</th>
<th>Evaluation title: Asfotase alfa for treating paediatric-onset hypophosphatasia</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asfotase alfa is recommended as an option for treating the bone manifestations of hypophosphatasia, only:</td>
<td>1.1, 5.40</td>
<td></td>
</tr>
<tr>
<td>• in people with perinatal- and infantile-onset disease and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• for the duration of, and within the conditions set out in, the proposed managed access agreement for asfotase alfa and</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The committee recognised that people in this population had the most severe forms of the disease and could potentially benefit considerably from treatment. It noted that the cost–consequence analysis showed that there was potential for a high quality-adjusted life year (QALY) gain in this group, although it came at a very high cost. Nevertheless, this population was associated with the fewest uncertainties and the greatest value for money. The committee was aware that the number of patients in this group, and hence the budget impact, were smaller than in the older populations. It considered that the financial risk to the NHS in this group was likely to be manageable, although it was aware that the proposed cost cap will not substantially reduce the cost of asfotase alfa during the period of the managed access agreement. The committee therefore recommended that NHS England and the company (Alexion Pharma UK) should further explore opportunities for short-term cost reduction of asfotase alfa for this group. The committee concluded that asfotase alfa should be recommended for people with perinatal- or infantile-onset hypophosphatasia for the duration of the managed access agreement. The committee stated that data gathered as part of the managed access agreement should provide information on how long treatment should continue, and when treatment could be stopped or the dose reduced, to inform a review of the guidance at the end of the 5-year period.

Asfotase alfa is not recommended for treating the bone manifestations of hypophosphatasia in children with juvenile-onset disease. The committee considered that asfotase alfa could provide important clinical benefits for some children with juvenile-onset hypophosphatasia. However, the cost of asfotase alfa is very high, and there are significant uncertainties about its long-term benefits. The committee considered that asfotase alfa had the potential to provide appropriate value for this group, but not under the conditions presented in the proposed managed access agreement and cost cap.

The committee was aware that this population was clinically very different from the perinatal- and infantile-onset population in terms of the need for treatment and the nature and size of the potential benefits. It also considered that the long-term benefits of asfotase alfa were considerably more uncertain in this population. It highlighted that this is a very heterogeneous group, and considered that the proposed managed access agreement did not identify those with the greatest clinical need. The committee noted the size of this group meant the budget impact of asfotase alfa would be substantially greater than for the perinatal- and infantile-onset group. It was concerned about the affordability of such a large investment, and the health benefits that may be displaced elsewhere in the NHS. Taking into account the clinical benefits of the treatment, alongside the value for money and budget impact, the committee recognised that asfotase alfa had the potential to provide appropriate value. However, it considered that the
conditions presented in the proposed managed access agreement and proposed cost cap as they stand were not sufficient to recommend asfotase alfa as an appropriate use of NHS resources.

Asfotase alfa is not recommended for treating the bone manifestations of hypophosphatasia in adults with juvenile-onset disease.

The committee highlighted that the benefits of asfotase alfa in this population were considerably lower than in other groups, but the cost of treatment remained high. It considered that asfotase alfa did not provide value for money in this population. The committee was also aware of the uncertainties in the size of this population, and that an increase in the population size would substantially increase the financial burden to the NHS. The committee highlighted that the need for treatment with asfotase alfa varied considerably within this group, and considered that the proposed managed access agreement did not identify a specific group for whom the clinical need is greatest or who would benefit the most from asfotase alfa treatment. The committee concluded that it could not recommend asfotase alfa for adults with juvenile-onset hypophosphatasia.

### Current practice

<table>
<thead>
<tr>
<th>Nature of the condition, including availability of other treatment options</th>
<th>Paediatric-onset hypophosphatasia is a 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.</th>
<th>5.1–5.3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>The committee concluded that a treatment that meets goals such as reducing mortality and pain would be highly valued because there are currently no treatments available that specifically prevent or delay the progression of hypophosphatasia.</td>
<td></td>
</tr>
</tbody>
</table>

### The technology

<p>| Proposed benefits of the technology | Asfotase alfa is the first therapy that specifically targets the underlying cause of hypophosphatasia, so the clinical experts considered it to be a step change in the management of paediatric-onset hypophosphatasia. | 5.4 |</p>
<table>
<thead>
<tr>
<th><strong>Adverse reactions</strong></th>
<th>Most adverse events were considered unrelated to asfotase alfa treatment and were of mild intensity.</th>
<th>4.17</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical evidence</strong></td>
<td>Most of the company’s clinical trial evidence did not include a concurrent control group. The committee agreed that without a concurrent control group it was reasonable in the circumstances for the company to compare with natural history data.</td>
<td>5.6</td>
</tr>
<tr>
<td><strong>Uncertainties generated by the evidence</strong></td>
<td>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. The committee heard from the clinical experts that there was considerable uncertainty about how long treatment was likely to be appropriate after stabilising the condition in clinical practice. The treatment need for children and adults with juvenile-onset hypophosphatasia varied. 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 committee agreed that the company had not sufficiently defined the population with the greatest clinical need within its proposed managed access agreement.</td>
<td>5.6, 5.9, 5.10</td>
</tr>
<tr>
<td><strong>Impact of the technology</strong></td>
<td>Asfotase alfa improved the probability of survival in perinatal- and infantile-onset hypophosphatasia compared with best supportive care. Although there was considerable uncertainty around robustness and the precise size of the treatment benefit, the results of the trials generally suggested that asfotase alfa was associated with clinically meaningful improvements across a range of outcomes when compared with baseline. However, the company presented evidence that quality of life gains from asfotase alfa treatment reduce as the age of starting treatment increases.</td>
<td>5.5–5.7, 5.28</td>
</tr>
<tr>
<td><strong>Cost evidence</strong></td>
<td>The committee discussed the company’s cost–consequence model and budget impact analysis.</td>
<td>5.12–5.30</td>
</tr>
<tr>
<td><strong>Availability and nature of evidence</strong></td>
<td>The committee identified the following uncertainties:</td>
<td></td>
</tr>
<tr>
<td>assumptions and inputs in the economic model and budget impact analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>• It was difficult to estimate the number of people with juvenile-onset hypophosphatasia in England, and consequently how many would be eligible for asfotase alfa treatment. But the committee noted the company’s estimate may be an underestimate, particularly for adults with juvenile-onset disease. This is because the starting, stopping and treatment continuation criteria proposed by the company were broad and not based on objective measures, and so would not adequately identify the group of people who would benefit most from treatment with asfotase alfa.</td>
<td>5.13</td>
<td>5.14</td>
</tr>
<tr>
<td>• The committee agreed that assumed 100% adherence provided the more plausible estimate for the budget impact.</td>
<td>5.10</td>
<td>5.16</td>
</tr>
<tr>
<td>• The committee preferred the company’s model structure to capture all symptoms of hypophosphatasia, but accepted that using 6-minute walk test (6MWT) distance to define health states was reasonable given the lack of evidence allowing for alternative structures.</td>
<td>5.19</td>
<td>5.30–5.33</td>
</tr>
<tr>
<td>• There were important differences in costs and outcomes for perinatal- and infantile-onset hypophosphatasia compared with juvenile-onset hypophosphatasia.</td>
<td>5.22</td>
<td></td>
</tr>
<tr>
<td>• Using natural history data that attempted to adjust for the potential biases was appropriate in the economic modelling.</td>
<td>5.24</td>
<td></td>
</tr>
<tr>
<td>• Costs of intensive care were reasonable, but associated with uncertainty given the resource use data were not transparent.</td>
<td>5.26</td>
<td></td>
</tr>
<tr>
<td>• It was more appropriate for the company to include a discount rate of 3.5% in its base-case analysis.</td>
<td>5.27</td>
<td></td>
</tr>
<tr>
<td>• Probabilistic sensitivity analysis suggested that the results of the cost-consequence analysis were not very stable and were therefore associated with considerable uncertainty, particularly for the estimation of QALY gains.</td>
<td>5.25</td>
<td></td>
</tr>
</tbody>
</table>

**Incorporation of health-related quality-**

<table>
<thead>
<tr>
<th>Incorporation of health-related quality-</th>
<th>The committee heard from the patient experts that the health-related quality of life of a child with</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5.25</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
of-life benefits and utility values

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?

- Hypophosphatasia can be substantially lower than that of a child without hypophosphatasia of the same age. The committee concluded that the mean utility values used in the company’s model were reasonable estimates for the 6MWT health states.
- 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.

Cost to the NHS and PSS

- The committee was aware that the company did not present a breakdown of the budget impact analysis for different age groups. However, taking into account the number of people in these age groups and the increase in the cost of asfotase alfa as people get older, the committee considered that the budget impact of asfotase alfa would be substantially larger in children and adults with juvenile-onset hypophosphatasia than in children with perinatal- and infantile-onset disease, despite the proposed cost cap. The committee further considered that, because the number of children and adults with juvenile-onset disease was underestimated, the budget impact in these groups would also be larger than the company’s estimate.
- The number of people in the perinatal- and infantile-onset disease group, and hence the budget impact, were smaller than in the older populations. The committee considered that the financial risk to the NHS in this group was likely to be manageable, although it was aware that the proposed cost cap will not substantially reduce the cost of asfotase alfa during the period of the managed access agreement.
- The committee believed the company’s proposed managed access agreement did not identify people in the juvenile-onset disease group with the greatest clinical need and also underestimated the number of people eligible for treatment. Therefore the committee believed that the company’s budget impact and cost–consequence model substantially underestimated the costs associated with asfotase alfa compared with best supportive care for juvenile-onset hypophosphatasia.
<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value for money</td>
<td>The committee recognised that people with perinatal- or infantile-onset disease had the most severe forms of the disease and could potentially benefit considerably from treatment. It noted that the cost–consequence analysis showed that there was potential for a high QALY gain in this group, although it came at a very high cost. Nevertheless, this population was associated with the fewest uncertainties and the greatest value for money. The committee was aware the juvenile-onset group is larger and clinically very different from the perinatal- and infantile-onset population in terms of the need for treatment and the nature and size of the potential benefits. It also considered that the long-term benefits of asfotase alfa were considerably more uncertain in this population. The committee noted asfotase alfa could provide important clinical benefits and provide value for money for some children with juvenile-onset hypophosphatasia but that the proposed managed access agreement did not adequately identify those with the greatest clinical need. For adults with juvenile-onset disease the committee highlighted that the benefits of asfotase alfa in this population were considerably lower than in other groups, but the cost of treatment remained high even with the company’s proposed cost cap. It concluded considered that asfotase alfa did not provide value for money in this population.</td>
</tr>
<tr>
<td>Impact beyond direct health benefits and on the delivery of the specialised service</td>
<td>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.</td>
</tr>
</tbody>
</table>

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 and the company’s proposed stopping criteria did not identify people with the greatest clinical need for continued treatment.
Overall, no major changes in staffing and infrastructure would be needed at the 3 specialist centres in England currently treating hypophosphatasia if asfotase alfa was made available.

### Additional factors taken into account

| Access schemes | The committee considered the proposed managed access agreement and the price cap submitted by the company but noted this had not been finalised with NHS England.
It noted that the company’s proposal that all babies with perinatal- and infantile-onset hypophosphatasia would be eligible for treatment was reasonable considering the impact of hypophosphatasia on this population.
It considered that the proposed criteria for starting, stopping and continuing treatment were broad and not based on objective measures, and so would not adequately identify the group of people with juvenile-onset hypophosphatasia who would benefit most from treatment with asfotase alfa.
It also concluded that the data collection and monitoring plan proposed in the revised managed access agreement was not sufficiently detailed and had a number of limitations.  |
| Equalities considerations and social value judgements | No equality issues were raised during the evaluation. |

### Implementation

#### 6

**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](https://www.gov.uk/government/publications/nice-constitution-and-failures-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

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.

6.3 The company has proposed that asfotase alfa will be available to the NHS with an annual per-patient price cap. The size of the price cap is 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 proposed cost cap should be directed to [NICE to add details at time of publication]

7 Proposed review of guidance

7.1 NICE proposes that the guidance on this technology will be considered for review 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Jackson
Chair, highly specialised technologies evaluation committee
September 2016
8 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.

**Martyn Burke and Thomas Strong**

Technical Analysts

**Linda Landells and Ian Watson**

Technical Advisers

**Leanne Wakefield and Jenna Dilkes**

Project Managers

**Sheela Upadhyaya (from November 2015)**

Associate Director

ISBN: To be added by editor before publication