NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGY

Asfotase alfa for treating paediatric-onset hypophosphatasia(review of HST6) [ID3927]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD)**

2. **Consultee and commentator comments on the Evaluation Consultation Document** from:

   - **Alexion**
   - **British Paediatric & Adolescent Bone Group**
   - **Metabolic Support UK**

3. **Comments on the Evaluation Consultation Document from experts:**
   - Mel Williams , Patient Expert

4. **Comments on the Evaluation Consultation Document received through the NICE website**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)

Highly Specialised Technologies

Response to consultee, commentator and public comments on the Draft Guidance Consultation

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

NICE National Institute for Health and Care Excellence

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Consultation on the evaluation consultation document – deadline for comments 5pm on 25 November 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. 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 clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Alexion Pharma UK Ltd.
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Hazel Dawson

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Provisional recommendation Alexion is pleased to have received a positive recommendation for perinatal-/infantile-onset patients with hypophosphatasia (HPP), although we would like to point out that the definition of perinatal/infantile onset (onset of symptoms before the age of 6 months) in the issued ECD is different to what had been agreed (as relevant to the UK medical practice) between NICE, NHSE, Clinical Experts and Patient Groups in the previous appraisal – the agreed definition then being patients presenting with symptoms of HPP before the age of 12 months. Therefore, the current provisional recommendation excludes patients between the age of 6-12 months that may have the life-threatening form of HPP and would benefit from asfotase alfa treatment. Alexion is disappointed that the Committee was minded not to recommended treatment for patients with juvenile-onset disease, despite evidence of clinical benefit from a 5 year managed access programme alongside testimony from both patient representatives and clinical experts of the benefits of treatment in this population. Restricting the recommendation to people with perinatal-/infantile-onset hypophosphatasia would result in a large proportion of UK paediatric-onset HPP patients not being able to access asfotase alfa in future. Of the 35 people with paediatric-onset HPP included in the Managed Access Agreement (MAA) analyses, [redacted] have juvenile-onset HPP. In addition, [redacted] had unknown onset. A negative recommendation from NICE would thus mean that [redacted] of the people who have benefited from access to treatment in the MAA to date would no longer be able to receive this life-changing treatment. As, the only available disease-modifying treatment option for HPP, the patient organisation submission from Metabolic Support UK highlighted the enormous impact that receiving asfotase alfa under the MAA has had on the lives of people with HPP, including those with juvenile-onset disease. For example, patients reported requiring fewer medical appointments, being weaned off a number of different medications (such as anti-seizure medication), reduction in fractures, marked improvements in mobility and mental health improvements (the recent survey conducted by Metabolic Support showed 83.3% of patients see fewer medical professionals and 100% saw an improvement in mobility). Restricting the recommendation will be a huge disappointment to this subset of patients who have benefited from asfotase alfa treatment over the past 5 years. The patient organisation submission also highlighted that caregivers and families of patients also experienced reduced burden and improved quality of life with asfotase alfa treatment. Alexion would like to ensure that people with juvenile-onset hypophosphatasia are able to benefit from ongoing treatment with asfotase alfa and are not excluded from the recommendation. As per NICE's request and as part of this response, Alexion has therefore submitted additional data specific to this subgroup. In addition, to address Committee concerns about the cost-effectiveness of asfotase alfa in this population, Alexion is also increasing the simple discount offered in its patient access scheme to [redacted] Alexion hopes the additional data along with the additional discount offered will help support a final positive recommendation.
2	Clinical effectiveness in juvenile-onset patient population As previously highlighted during technical engagement, the MAA was established in collaboration with NHSE, NICE, clinical experts and patient advocates, and was not set up to address differences in outcomes for patients with perinatal-/infantile-onset and juvenile-onset

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	hypophosphatasia. Eligibility criteria were rather based on the age of patients at the time of presentation at the designated treatment centres and their presenting symptoms relative to defined treatment qualification criteria. The only requirement was that patients had paediatric onset hypophosphatasia, in line with the MHRA approved license for asfotase alfa. Data analysis by age of onset was not one of the parameters specified within the MAA Data Collection & Sharing Agreement. Moreover, 6/7 asfotase alfa clinical studies included in the dossier were not designed to address patients' outcomes based on the age of HPP symptoms onset. Alexion is therefore disappointed that NICE has requested a breakdown of the data from the MAA and the asfotase alfa clinical studies in this way. As previously highlighted during EAG clarification questions, it is challenging to find (from natural history studies) a matching BSC population of HPP patients for each population, and the three available natural history studies included in the dossier do not contain data for all relevant endpoints, so a comparison for all endpoints would not have been possible. During the evaluation process, it was recommended that the Global HPP Registry (ALX-HPP-501) be used as a source of comparative (i.e., BSC) data, using appropriate methods for adjusting for potential confounders according to the methods described in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 17[1]. As Alexion described during the evaluation process, patients treated with asfotase alfa under the MAA and those never-treated in the registry differ significantly in disease severity at enrolment, which would confound comparative analysis. Specifically, the populations differ in the impact of HPP on mobility and pain, two factors that underlie disease severity as it is defined in the start criteria for treatment under the MAA for patients aged ≥5 at start of treatment, as summarized in the additional supporting document. Nonetheless, Alexion would like to provide all of the available data to attempt to address the uncertainties and have therefore provided analyses of data specific to juvenile-onset hypophosphatasia collected during the managed access agreement, the asfotase alfa clinical trial programme and from the Global Hypophosphatasia Registry (ALX-HPP-501), for all relevant outcomes (Request 1), and a comparative efficacy analysis of asfotase alfa and BSC in people with juvenile-onset hypophosphatasia for all relevant outcomes (Request 2). These data are provided in the additional supporting document.
2	Application of Carer disutility Section 3.14 of the ECD states '*They considered that the use of the EAG's approach in the model was technically correct but produced the counterintuitive outcome mentioned above and preferred to consider this aspect qualitatively*'. While Alexion agrees with the Committee that the EAG's approach, which resulted in counterintuitive outcomes (implying that caregivers prefer the death of their child over caring for them), Alexion strongly believes that the impact on caregivers should be considered within the analysis. Patient and carer testimonies that were provided in the committee papers and during the committee meeting provide strong evidence of the tremendous burden felt by caregivers and the inevitable impact on their quality of life. The company used disutility data from Duchenne's muscular dystrophy, and the Committee highlighted that disutility from Duchenne's muscular dystrophy may underestimate the impact on carers in hypophosphatasia, due to events such as seizures being more common in people with hypophosphatasia. Moreover, there is clear precedent from other HSTs where carer disutility has been quantitatively applied in cost-effectiveness analyses and accepted by Committee, regardless of uncertainties

[1] Faria R, Alava MH, Manca A, Wailoo A, editors. NICE DSU TECHNICAL SUPPORT DOCUMENT 17: The Use of Observational Data to Inform Estimated of Treatment Effectiveness in Technology Appraisal: Methods for Comparative Individual Patient Data. 2015. URL: https://www.sheffield.ac.uk/media/34204/download?attachment

surrounding the data and methodology. For example, a paper by Pennington 2020 reviewed carer health-related quality of life in NICE appraisals and found that in 11 out of 16 appraisals that included health-related quality of life, the Committee felt that it should be included in the base case.[2] In addition, the recent HST for selumetinib for treating symptomatic and inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in children aged 3 and over (HST20) stated that the committee accepted the application of applying disutility to 1 carer.[3] Furthermore, the previous HST submission for Ataluren for treating Duchenne's muscular dystrophy (HST3) included a caregiver disutility of 0.11, applied to two caregivers (total of 0.22).[4] This is higher than the disutility proposed by the EAG for hypophosphatasia, where a disutility of -0.11 was applied to the worst health states, but as the model re-weights the caregiver disutility associated with the less severe health states, the values used across the other health states in the EAG model are considerably lower than those used in HST3 (ranging from -0.03 to -0.11), please see the table below for a comparison of the different caregiver disutilities used in the company and EAG preferred analysis. As stated above, the Committee highlighted that disutility from Duchenne's muscular dystrophy may underestimate the impact on carers in hypophosphatasia, therefore both the company and EAG analysis may underestimate the impact on carers quality of life. Also, the NICE methods state that health effects for carers should be considered in section 4.3.17: *'Evaluations should consider all health effects for patients, and, when relevant, carers. When presenting health effects for carers, evidence should be provided to show that the condition is associated with a substantial effect on carer's health-related quality of life and how the technology affects carers.'*

As such, given the patient testimonials and methods outlined by NICE, Alexion believe it is wholly appropriate to quantitatively capture the impact on carers in the asfotase alfa cost-effectiveness model, even if it may underestimate the true burden on carers. In addition, Alexion agrees with the Committee that the approach adopted by the EAG can produce counterintuitive outcomes, as acknowledged by Committee. However, while imperfect, as there are no expected differences in survival for the juvenile-onset population, the EAG approach can be applied.

Health state	**Utility value in company analysis**	**Utility value in EAG analysis**
No invasive ventilation	-0.09	-0.06
Invasive ventilation	-0.17	-0.11
SLI	N/A	N/A
SLII	-0.05	-0.03
SLIII	-0.09	-0.06
SLIV	-0.17	-0.11

3 Drug wastage

[2] Pennington BM. Inclusion of carer health-related quality of life in National Institute for Health and Care Excellence appraisals. Value in Health. 2020; 23(10):1349-57.

[3] National Institute for Health and Care Excellence (NICE). Highly specialised technologies guidance (HST20): Selumetinib for treating symptomatic and inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in children aged 3 and over. 2022. Available at: https://www.nice.org.uk/guidance/hst20

[4] National Institute for Health and Care Excellence (NICE). Highly specialised technology appraisal guidance [HST3]: Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene. 2016. (Updated: 20 July 2016) Available at: https://www.nice.org.uk/guidance/hst3.

Asfotase alfa for treating paediatric-onset hypophosphatasia(review of HST6) [ID3927]

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	Section 3.16 of the ECD states *'The committee considered that the EAG's approach aligns with the recommended dosage in the summary of product characteristics. They concluded that drug wastage using rounding up should be included in the model'*. In contrast to the EAG, Alexion adopted a rounding down approach to asfotase alfa dosing in the cost-effectiveness model based on input from clinical experts who indicated such an approach would be considered to minimise unused drug and reduce drug wastage. Given the presence of clinical experts in the Committee meeting, Alexion was surprised that the Committee did not consult the experts on this point. Indeed, this topic was not discussed in the Committee meeting with clinical experts at all. Consequently, Alexion believes the approach to drug dosing should be reconsidered in order for a fair decision on drug wastage to be made that is reflective of clinical practice.
4	<u>Updated base case results</u> Alexion have updated the cost-effectiveness model in accordance with the request from NICE, with the following updates: • the disease severity of the starting cohort in the model is based on data from people with juvenile-onset hypophosphatasia (the baseline distribution across health states is specific to people with juvenile-onset hypophosphatasia) • data informing the severity level transitions is specific to people with juvenile-onset hypophosphatasia for both the asfotase alfa and best supportive care groups (6MWT regression analyses) The updated severity level distributions are shown below, demonstrating that the restricted baseline distribution is similar to the overall paediatric onset population.

<u>Paediatric-onset HPP</u>

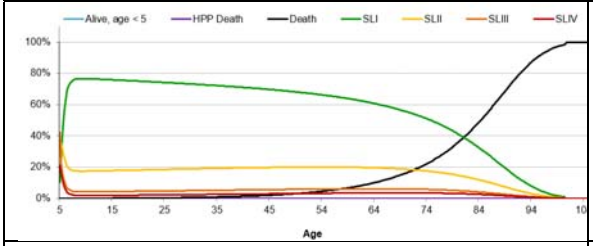
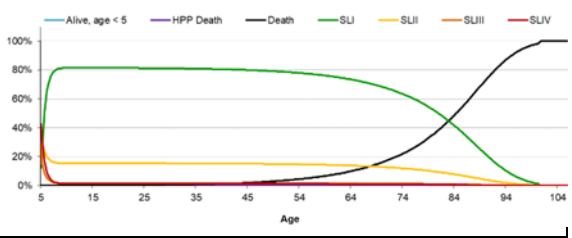
	SL1	SL2	SL3	SL4	Total
N	5	7	14	20	46
%	10.87	15.22	30.43	43.48	100.00

<u>Juvenile-onset only</u>

	SL1	SL2	SL3	SL4	Total
N	4	5	10	14	33
%	12.12	15.15	30.30	42.42	100.00

The new base case results for the juvenile-onset population generates [redacted] incremental QALYs and £[redacted] incremental costs, resulting in an ICER of £244,434 without QALY weighting, and £81,478 with QALY weighting.

The Markov traces for asfotase alfa and BSC remain similar compared to the original model, as shown in the graphs below.

Markov trace for asfotase alfa, original model (including all paediatric-onset population)	Markov trace for asfotase alfa, updated model (restricted to juvenile-onset population)
	
Markov trace for BSC, original model (including all paediatric-onset population)	Markov trace for BSC, updated model (restricted to juvenile-onset population)

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	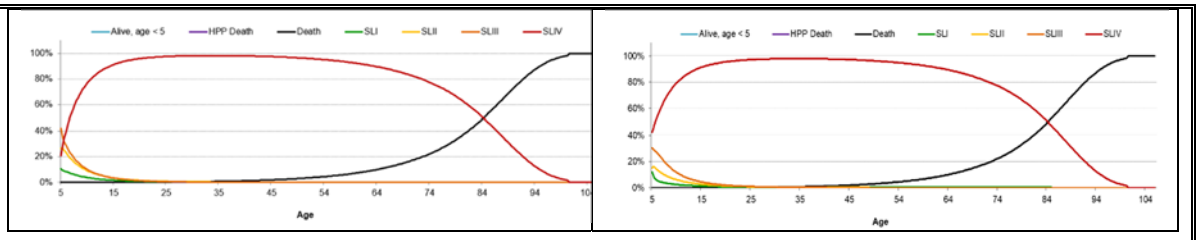 The updated base case results are fully detailed in the additional supporting document.
5	Factual accuracy check The following points within the ACD have been noted as factually inaccurate or not fully reflective of the evidence base. We would request that for future documents the text is corrected. • Section 3.1, page 6, it is reported that *"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".* This is not correct, as TNSALP is the enzyme not the gene and mineralisation is not just the process in which calcium and phosphorous are deposited in developing bones and teeth. It would be more accurate to state "*Hypophosphatasia is a genetic disorder caused by mutations in the ALPL gene, which in turn causes a deficiency in tissue non-specific alkaline phosphatase (TNSALP) enzyme activity. This results in deficient bone mineralisation, a process in which calcium and phosphorous are deposited in developing bones and teeth."* • Section 3.1, page 7, it is reported that *"The committee concluded that the morbidity and mortality associated with paediatric-onset hypophosphatasia varies depending on the age that symptoms start."* Although this is the opinion of the Committee this is not technically accurate as age at onset is not the only factor to consider. Alexion request that this is changed to reflect the fact that mortality associated with paediatric-onset HPP varies depending on the age that symptoms start whereas HPP associated morbidity varies patient to patient and may progress over a patient's lifetime. • In section 3.4, page 10, it is reported that *"ENB-009-10, a randomised, 24-week concurrent control study in 19 people of 13 years to 66 years with hypophosphatasia (18 of 19 people had paediatric-onset hypophosphatasia) followed for up to 5 years".* This is not correct, as the ENB-009-10 study included patients aged 13 years to 65 years. Alexion request that that this is changed to *"ENB-009-10, a randomised, 24-week concurrent control study in 19 people of 13 years to 65 years with hypophosphatasia (18 of 19 people had paediatric-onset hypophosphatasia) followed for up to 5 years".* • In section 3.4, page 11, the outcomes included in the trials and real-world evidence studies are reported. Mobility assessments are not currently included in this list. Mobility assessments such as the 6MWT are key outcomes, therefore, please can this list be updated to include mobility assessments. • In section 3.5, page 11, it is reported that *"In 2 of the studies presented by the company (UK MAA data and ENB-009-10), results were presented by age at study entry: under 18 years or 18 years and over."* This is not accurate for the ENB-009-10 trial. All efficacy and safety data presented in the submission were for the combined population (n = 19) that included 18 patients with paediatric-onset hypophosphatasia and 1 patient with adult onset-hypophosphatasia. Only outcomes specific to adolescent patients (e.g. growth) and the prespecified subgroup data were presented for patients under 18 years or 18 years and over. Therefore, please can this text be updated to reflect this.

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	• Section 3.8, page 14 states that "the experts said that there may have been improvements in respiratory care in the last 20 years that could have influenced survival'. Alexion would like to request a change to this statement, as the current wording suggests that respiratory care changes could reduce mortality, but this is not the case and is not what the clinicians said. The clinicians clearly stated that although some advances in respiratory care have been made in the last 20 years, the influence on survival is not possible unless the bone phenotype of the disease (bone mineralisation that allows ribcage development) is corrected with asfotase alfa treatment. • In Section 3.12, page 18, the ECD states '*However, it noted that in the juvenile-onset hypophosphatasia model, transition probabilities should be based on data specific to this subgroup*.' This is not applicable to the probabilities for invasive ventilation as these are only relevant in the perinatal/infantile onset population. Given invasive ventilation is not relevant in the juvenile-onset population model, we suggest this sentence is inappropriate and should be removed from this section of the ECD. • In Section 3.19, page 22 Cost-effectiveness estimates), the ECD states '*The company's base case resulted in a probabilistic ICER of £39,069 per QALY gained in perinatal- or infantile-onset hypophosphatasia with the QALY weighting applied.*' This is incorrect as this is based on the PAS submitted during technical engagement with the inclusion of the price reduction on loss of exclusivity, whereas Alexion agreed at the technical engagement stage, prior to the Committee meeting, that the loss of exclusivity should be removed. The correct ICER for the company base case is £84,439. • In section 3.20, page 23, the ECD states '*The company's base case resulted in a probabilistic ICER £46,519 per QALY gained in juvenile-onset hypophosphatasia with the QALY weighting applied.*' This is incorrect as this is based on the PAS submitted during technical engagement with the inclusion of the price reduction on loss of exclusivity, whereas Alexion agreed at the technical engagement stage, prior to the Committee meeting, that the loss of exclusivity should be removed. The correct ICER for the company base case is £99,878. • Section 3.21, page 24 states "The company noted that the current UK managed access agreement excludes some adults with paediatric-onset HPP from accessing asfotase alfa." This is not accurate. During the Committee meeting, the company highlighted that Slide 56 of the committee slides contained a factual inaccuracy, stating that "the current UK MAA excludes adults with paediatric onset HPP accessing AA". This was highlighted as factual inaccuracy as the UK MAA does include adults with paediatric onset HPP. However, this has now been mis-represented in the ECD as per the statement on page 24. The company would like to request that the original factual inaccuracy in the Committee slides is corrected and this further error is also removed from the ECD.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is

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submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology evaluation (section 3.1.23 to 3.1.29) for more information.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the evaluation consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**British Paediatric & Adolescent Bone Group**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	I confirm that none of the members or the organisation has any direct or indirect funding links to the tobacco industry
Name of commentator person completing form:	[**Chair, British Paediatric and Adolescent Bone Group**]

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply……..
1	We are pleased to note that NICE has recommended perinatal and infantile-onset form of hypophosphatasia be eligible for treatment with asfotase alfa
2	We are however concerned that this recommendation implies that symptomatic children and adults with juvenile-onset forms of hypophosphatasia will not be eligible for treatment with asfotase alfa
3	In our clinical practice, we find that HPP in children is a continuum with overlap between perinatal-onset, infantile-onset and juvenile-onset forms. It has been accepted in the medical literature that the severity of the juvenile-onset form ranges from mild to severe and that severe juvenile-onset form can present with skeletal deformities, severe pain, a significant reduction in mobility, and other morbidities such as craniosynostosis, even though these are most typically associated with perinatal-onset and infantile-onset HPP. [**(1) Mornet E**. Hypophosphatasia. *Orphanet J Rare Dis.* 2007 Oct 4;2:40. doi: 10.1186/1750-1172-2-40 **(2) Whyte MP**. Hypophosphatasia - aetiology, nosology, pathogenesis, diagnosis and treatment. *Nat Rev Endocrinol.* 2016 Apr;12(4):233-46. doi: 10.1038/nrendo.2016.14. **(3) Whyte MP**, *et al.* Hypophosphatasia: validation and expansion of the clinical nosology for children from 25 years' experience with 173 pediatric patients. *Bone*. 2015 Jun;75:229-39. **(4) S.S. Seshia**, *et al* Myopathy with hypophosphatasia Arch Dis Child, 65 (1990), pp. 130-131]. We are therefore concerned that the demarcation made explicit by the draft recommendation in the ECD neither recognises the reality of the distribution of severity of disease within the population with HPP, nor the clinical reality faced by medical teams caring for individuals with HPP. We are concerned that not offering Asfotase alfa to symptomatic patients with Juvenile-onset HPP (pain, myopathy, etc) will lead to a significant negative impact on their and their carer's Quality Of Life.
4	Milder forms of juvenile-onset HPP do not require treatment. Currently, there is a robust mechanism in the NHS to treat the most severe by review of such cases by the National Authorisation Panel (NAP) established by the NHS. This panel reviews all cases submitted to them on the basis of the following parameters: clinical features, biochemical and genetic abnormalities, skeletal radiographs, pain assessment by an independent tertiary pain team, objective assessment of mobility (6-minutes-walk test and Bleck's score) and patient-reported outcome measures for quality of life of child and carers. In addition, this panel also monitors the outcome of the treatment and can advise NHS England to discontinue treatment if set targets for improvement are not achieved. We as clinicians have found this process of identifying Juvenile HPP patients suitable for asfotase alfa very useful and would strongly advocate for this to continue.
5	We have noted that the committee has considered that asfotase alfa has not been compared with the best supportive care in the juvenile-onset hypophosphatasia population. We accept that there is a gap in evidence for this. In clinical trials, patients recruited in the registry, and in the current Managed Access Agreement (MAA), patients affected with significant skeletal changes and symptoms of hypophosphatasia, and who fail to respond to supportive care, have been treated with asfotase alfa. The current best supportive care for these patients includes pain relief with analgesics, referral to a pain team, occupational therapy, physiotherapy, and clinical psychology input. Only those who fail to respond to the best supportive care are referred to NAP for approval for treatment under NHS. In paediatrics, very few children in England and Wales with juvenile-onset HPP have undergone NAP approval (only 2 in total out of 4 referred to NAP over 5 years which is fewer than 5% of all juvenile-onset HPP presenting in childhood in England and Wales). Clinically they have received asfotase alfa and have responded well with improvement in their pain and motor function. It is however difficult to compare the best supportive care in those with juvenile-onset who did not receive treatment with those who did as there is such a range of severity of disease within this group and the groups who have had a treatment approved have, almost by definition, much greater severity of the disease.

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6	The committee has suggested that cost-effectiveness estimates in juvenile-onset would be highly uncertain. Given our knowledge and experience of the most severe cases of juvenile-onset HPP, we believe that the size of the benefit of treatment in this small subgroup, if an appropriate comparison were made, would be such that we would be hopeful that the technology could be cost-effective for the NHS if delivered within the context of a highly specialised service with national authorisation panel overseeing initiation and monitoring of their progress for the continuation of treatment. We therefore strongly support the committee's recommendations for clarification and analyses as outlined in section 1.3 of the consultation document.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology evaluation (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the evaluation consultation document, please submit these separately.

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. 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 clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Metabolic Support UK**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**n/a**
Name of commentator person completing form:	

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are uncertain as to the reason why the committee is now at this late stage considering the subtypes of paediatric-onset Hypophosphatasia separately rather than as an umbrella term. This has been a huge surprise for us and presents immense difficulties for patients in the future looking to access the treatment. 35.7% of our survey respondents (November, 2022) did not know which form of paediatric-onset hypophosphatasia they have. The subtype is not something typically seen on medical records or shared with patients and it is difficult to prove, particularly for those older patients where records from childhood are scarce or unclear. Hypophosphatasia is described as a continuum with the subtypes based on age and severity and reliant on a specialist with knowledge in this area to determine using their own perspective of where the patient fits most appropriately. One patient shared their insight saying “this is a problem for many of us with HPP. When initially diagnosed the specialist often doesn’t know about the condition or your history and they define you by the age you receive the diagnosis. Then all letters etc., that come through from consultants always just say Hypophosphatasia - they never state the differentiations as specified by NICE. The consultants have to see you on numerous occasions to gather your history and then make an informed decision on the age of onset of Hypophosphatasia. This can take some time”. Another told us “my daughter had a formal diagnosis of Hypophosphatasia by letter from NHS but at this point no classification by infantile-onset or juvenile onset - maybe this was a later classification introduced as more was known about Hypophosphatasia?... this was after previous concerns raised regarding early shedding of baby teeth and reduced mobility / late walker that we as parents raised via GP”. Many of the early signs and symptoms are missed or dismissed as being growing pains or other mild insignificant problems that would likely resolve with time. In general, parents are not aware of hypophosphatasia let alone the symptoms unless it is already known within the family and so whilst symptoms may be present and discussed with health professionals there would be no known reason for them to ensure they were recorded on medical records as proof towards needing a future treatment. For many it is only with hindsight that symptoms have been apparent from a much younger age than first thought. The draft guidance means a further burden is placed on parents or carers or the patients themselves to prove this. One parent told us their views: “The line drawn between infantile and juveille onset HPP at 6 months is arbitrary. In retrospective, my daughters did show symptoms before 6 months , but my eldest daughter was only formally diagnosed at 18 months - as it took that long to get the issue escalated via health visitor / GP to specialist waiting list.”
2	We do not feel that the current draft guidance is consistent with the existing statements within the Managed Access Agreement. The Managed Access Agreement states the following “Although infantile onset HPP is defined as HPP which presents up to the age of 6 months clinician consensus is that patients with symptoms and signs consistent with HPP presenting below the age of 1 year of age are most likely to have perinatal or infantile onset HPP. All perinatal- and infantile-onset HPP cases, up to one year of age, who meet the start criteria above should be initiated on asfotase alfa therapy as soon as practical.” Therefore we feel that the clinical opinion, which has been both applied and accepted in the Managed Access Agreement has not been taken into consideration for draft guidance.
3	We believe there has been a lack of understanding and insight into the symptoms experienced by those in what is considered to be the “juvenile-onset” age category**.** Symptoms are described as being progressive, many cases begin with mild and insignificant symptoms but become worse following the onset of fractures. For children, this means that symptoms can progress and mobility deteriorate within a short space of time. This has implications on education and friendships. One parent told us about the progression of symptoms in their child “He couldn't even walk a short distance, he couldn't play like a normal child due to chronic daily pain, increased migraines,

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	increased fractures, auditory processing delays, speech impairment; and by age 11, I watched my son barely be able to walk up the stairs becoming debilitating and was also bullied in school for being "different" and having to "sit out" from activities." Another described their experiences: "We found out he had HPP when he was two and had a tooth fall out with the root attached. He'd had an autism diagnosis at 18 months and was nonverbal. When he would walk, he seemed like a little drunk man...that's the best way to describe it. He would take a few steps, sway or fall, take a few more and stop. He couldn't do any activity for very long…. All his Autism symptoms ended up being related to HPP. Most was due to muscle fatigue and lambdoid craniosynostosis. He would screech, not make eye contact, he seemed to be in pain all the time. That's just mothers intuition. He would choke often on food. We thought it was sensory, but it was oesophageal weakness." Deterioration can also occur in adulthood, we spoke to adult patients with paediatric-onset hypophosphatasia who would most likely be viewed as having the juvenile onset form. One told us "I never broke a bone as a child, but always had extreme fatigue, excessive illness and pain. My alkaline phosphate was always low. I just thought I was tired. One day in my late 20's I knew there was more wrong. I couldn't climb the stairs anymore or walk across the room without excessive pain and struggle. I also couldn't sleep at night because my bones ached." Similarly another patient who was experiencing progressive lack of mobility told us they were referred to a rheumatologist for further investigation as to why osteoarthritis was so bad at such as young age. "I also was feeling more and more fatigued and was moving slower and slower despite trying to stay active" "Non-steroidal anti-inflammatory drugs could take the edge of the pain but it was a struggle to keep doing all the things I needed to do. I felt like I wasn't performing to the same level at work and had such anxiety and brain fog much of the time." A further patient told us that in childhood, their symptoms were largely recurrent dental problems, migraines, clumsiness, and bone pain. The first fracture occurred in early adulthood and was followed by an asymptomatic period before deterioration occurred and musculoskeletal problems affecting the joints multiplied requiring therapies, surgeries, and orthotics, not just to deal with the joints but to manage fractures too which did not heal. Through our discussions it also became important for us to emphasise that the fractures seen in hypophosphatasia are not akin to normal fractures. They do not heal like normal fractures, taking an excessive amount of time and additional support. Some said the long-term impact of fractures and the process of recovery itself leaves patients vulnerable to other secondary problems, as you lose further mobility, become less independent, and then require even more support from the NHS. One patient described care prior to Strensiq as being like an endless cycle. Fractures each resulted in a year spent on crutches and then 4-5 months later a spinal fracture left them bed bound in hospital for many months, requiring long term support and homecare to rehabilitate. The patient described their experiences as being "just as devastating for me as recovering from a heart attack, in terms of impact". The experiences faced by this patient left them close to a mental breakdown during their period in hospital and even now recollection of the impact of the fractures caused relived trauma, meaning our call was brought to a close. The impact on mental health is significant, there is a great deal of raw emotion that is experienced daily and this has become extremely evident during this process through discussions and through case studies. Many have shared their experiences of requiring counselling, anti-depressants, and cognitive behavioural therapy to help them to deal with anxiety or depression caused by the impact of symptoms. We were told "prior to getting the treatment I struggled to get through each day… after trying every form of pain control I found that alcohol worked the best, but was totally unsustainable and incompatible with living life". Similarly "my sister was disappointed to wake up, not knowing how she would make it through another day." The impact of symptoms often means there is a huge feeling of disconnect with society, friendships, and relationships and this builds on feeling of anxiety and worry. Days out and spontaneity become more reduced with time with some saying that the effort or the recovery period afterwards just became too much and so opted to miss out on spending quality time with friends. Some also shared their feelings of being a burden to loved ones, others saying even those close to them could not comprehend the impact of fatigue. One shared their sense of expectation to contribute to society, to chores, to anything requiring time and energy but there is only

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	a limited amount that can be given and this leads to a sense of guilt and frustration. One patient told us about their journey up to Asfotase alfa becoming available "Up to that point I had broken 38 bones. From my femurs to my feet to my ribs to my right hand thumb to my wrist to my tibia. I was in constant pain, always searching for an answer and something to stop the pain. I tried chiropractic care, swimming (water therapy), physical therapy, a tens unit, pain medications, acupuncture, psychotherapy, orthotics, and rest. I was off work many days. I am a school teacher. I used a wheel chair, a walker and a cane throughout an 11 year span during the period of my bones breaking. I was depressed and raising 2 small children. Or at least I tried. I cried daily."
4	We do not feel that there has been enough consideration or discussion to determine what the term "best supportive care" means to patients and costs that this includes. Without treating the direct cause of the HPP, those adults with paediatric onset hypophosphatasia who are most likely to fall within the juvenile-onset category describe their healthcare as "just chasing symptoms". When we asked patients to rate the care that they received in terms of the impact on symptoms 76.9% rated this at 1-2, having no (61.5%) or little (15.4%) impact with respondents stating care being "no help at all, I've been left to myself and left to struggle", "Nothing helped, it was all trial and error", and a further stating "very little helped apart from nailing my bones back together when they fractured!!" Care is often disjointed and treatment based on symptomatic relief or surgery and rehabilitation for fractures. For the vast majority of patients and parents carers, when we asked about best supportive care, many said that they felt it was simply non-existent or nowhere near enough to alleviate the symptoms. Patients report having tried various medications or multiple medications at the same time including: • Pain relief (paracetamol, morphine – patches and oral, tramadol, gabapentin, Co-codamol, codydramol, codeine phosphate /paracetamol) • Non-steroidal anti-inflammatory drugs (naproxen, indomethacin, celecoxib, etoricoxib, Meloxicam • Anti-rheumatic medications (hydroxychloroquine) • Antidepressants/pain relief (amitriptyline, duloxetine) • Gout medication (colchicine) • Headaches/migraines (sumatriptan) • Depression and anxiety: (propranolol, escitalopram, citalopram) • Supplements (Adcal D3, Strivit D3) • Other (prednisolone, omeprazole, buscopan, lansoprazole, medical cannabis, beta-blockers, betahistine, cetirizine, low-dose naltrexone) Therapies include physiotherapy, hydrotherapy, deep tissue massage, osteopathy, homeopathy, ultrasound therapy, shockwave therapy, acupuncture, chiropractor, podiatrist, nutrition-based management/therapy, cognitive behavioural therapy, counselling. One patient who accessed multiple of these told us that the NHS only offered one or two sessions of "virtual physiotherapy" which could be provided. It is important to note here that many of the medications also bring their own challenges through side effects. Through discussions with adult patients with paediatric-onset hypophosphatasia the pain relief medications were most problematic. Pain relief for many does not provide sufficient relief for bone pain but those who have such a high dose that does alleviate pain, we have heard from patients that it leaves them feeling "like a zombie". One patient told us that the morphine patch they were given was adequate at alleviating the pain but left them unable to function, unable to drive, work, or carry out tasks safely at home. So the choice had to made between this or being in constant pain and still going to work to ensure they could pay the bills and keep a roof over their head. It is a case for many where they are simply stuck. "I was "between a rock and a hard place" as they say. In addition to the many proven benefits of exercise for the general population, exercise could help me maintain a healthy weight to relieve loading on my bones, plus it could keep my muscles strong which support the long bones in my legs and prevent excess force from being transferred directly into the bone.

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However, I had reached a point where any form of exercise caused too much bone pain, and my fracture risk was too high." Asfotase alfa has been able to provide patients with a better ability to manage their symptoms, pain, and maintain their jobs and social lives. Since taking Asfotase alfa, 63%, including all those listing the most medications have seen vast reductions in the amount of medications taken and a reduction in therapies accessed.

In terms of medical appointments, some patients are attending more than 10 appointments per month to manage their condition. One patient told us they attend up to 21 appointments per month for pain relief and to alleviate joint pain. Two respondents gave us an insight into private costs of care, one paying approximately £5000 over the last 5 years and the second providing the following breakdown of costs:

- "4 x different rheumatologists. I have seen over 4 different private rheumatologists in the past 4 years. I have seen each one numerous times (3-5 times)…Each session is around £250 per consultation. total value = £4,000
- Shoulder Surgeon- seen over 6 times for consultations. Required various scans (imaging, shoulder surgery and frozen shoulder treatment)…Estimated cost = £15,000
- Gastroenterologist (seen 2x doctors over years with same tests)- 2x consultation plus tests (colonoscopy, endoscopy, stomach emptying test)…(unsure exact cost for tests).
- Sports consultant- seen 5 times (£200 per appointment) - required steroid injections =£1,500
- Orthopaedic consultant- self funded. 6 consultations (£300 each) + PRP x3 injections £4,800
- Knee Surgeon - 2x consultations £250 + MRI scan = £1,000
- Foot Surgeon- 3x consultations + MRI =£200 per appointment (unsure Imaging costs)
- Hip Surgeon - 2x consultations + Mri = £200 per appointment (unsure Imaging costs)
- GP (private) 4x consultations (£50 per session) =£250 (when NHS waitlist is too long)
- Also please note that I have not included prescription costs (NHS and Private)"

This is a staggering amount. For many paying privately and self-funding treatments is unachievable and for many does not alleviate symptoms. Most access some private care out of desperation despite this. Costs are clearly unsustainable, and with progressive loss of mobility and increase in pain those in work and currently able to pay private costs are facing the prospect of having to leave work due to declining health with NHS shouldering the future financial burden of these patients. Following use of Strensiq, 75% of patients ceased paying privately for their care or reduced the amount paid due to a decrease in symptoms.

In terms of attending appointments, these have reduced for many since taking Strensiq, "I haven't needed to visit my GP once since beginning Strensiq. I have only had to visit my Metabolic Specialist for monitoring purposes for the MAA. I have seen no other specialist over the past 3 years whilst on Strensiq". Another patient told us "I no longer am attending GP for different pain relief. As I now am on the only drug out there that can help and does help.". A parent told us they "Now only attend every 2-3 months with different specialties as treatment has improved symptoms"

Throughout UK healthcare the view is to treat early to prevent long term problems which become more significant and require more management. The draft guidance for those with the termed "juvenile-onset" forms of hypophosphatasia appears to contradict this. Patients are being left in limbo, constantly accessing different treatments and care which is both invasive and expensive and leads to a massive decline in the patients wellbeing which becomes a secondary problem. It is worth noting that 76.9% of patients who took our survey have started taking Asfotase alfa over 10 years after symptom onset, which means that symptoms and trauma has already occurred and is irreversible. Asfotase alfa does however, alleviate many of the symptoms such as pain and fatigue. For those future patients though who are diagnosed with juvenile-onset hypophosphatasia, Asfotase alfa will allow for their symptoms to be addressed prior to them becoming problematic, prior to them deteriorating and needing long-term management, and instead allows them to grow, develop, have social lives, go to work, and have a much more improved quality of life. Asfotase alfa gives them the freedom and ability to avoid the same experiences we hear from the adult patients taking Asfotase alfa today. "When I think of the endless doctor visits, tests, and unhelpful treatments prior to our

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	diagnosis and starting enzyme replacement therapy (Strensiq), all the pain, confusion, and the impact it had on our lives, all the money that was spent, I think it was a real shame we couldn't have started treatment earlier. Perhaps if we had gotten treatment earlier we could have avoided, or mitigated, the degeneration of our spines. Earlier treatment could have spared us a lifetime of depression, anxiety and brain fog. It could have spared us the pain of microfractures in our feet, and kept us from having to undergo surgeries to repair damage to muscles and tendons caused by calcium deposits." "The cost of Strensiq is very high for treating adults but not as much as the medical intervention and care that was needed yearly before starting Asfotase Alfa. The homecare I needed was 18 hours a day when I was in passive treatment of just casts to allow bones to heal. It was 24/7 care when I had surgery to stabilize the fractures and this was for 10 months at a time. I would be ok for 10 to 15 weeks and something else would break and the cycle would start again. The high cost and out of pocket cost were dramatic on my family and led to love ones to lose their jobs so they could take care of my daily needs... Strensiq is worth the excessive cost at first look but if you add up the multiple teams of doctors, prescriptions, hospital stays and home care takers yearly, you also have to consider the income loss to the family which puts more demand on the social system to house, pay for food and utilities." "Over the years once I have waited for months or sometimes years to see specialists/physios but once in the system I have had the best of care from the hospitals. I have had countless cortisone injections all over my body. I have had painful shockwave therapy on my shoulders, Achilles and plantar fascia. I have had high volume injections into my Achilles heels. I have had countless physio visits over the years until you reach the max allowed. The maximum sessions allowed on the NHS of acupuncture. Also numerous treatments with ultrasound therapy. When the symptoms become so severe and you have tried all of the above options you find that you need an operation to try and get some pain relief. I have had numerous operations: on my back and on my shoulders and elbow . Unfortunately the you have deal with the recovery following the operation together with ongoing severe pain in other parts of your body. This disease is systemic and relentless and you are never dealing with one area of pain. It is a vicious cycle and very traumatic to deal with time after time. There are times when you have had enough and mentally it is a huge fight to continue and it is during these periods that I have needed to pay for treatment to keep me sane or to help alleviate the symptoms of HPP whilst waiting to see specialists on the NHS. I feel the care received from my GP in prescribing pain relief and mental health solutions is very inadequate. GP's are not experts in the condition and so you feel alone with the diagnosis and have a constant battle to be seen by specialists at hospitals. It is a total nightmare and totally disheartening. You go in to a consultation with hope and all you are offered is another operation or invasive treatment. You leave in tears - it's a living hell! It is also terrible for the consultants who have no alternatives to offer unless you can access Strensiq."
5	For those with the perinatal and infantile forms, Asfotase alfa is of course a life-saving medication and we hope with the guidance they will continue to have access, However, the guidance does not support those children who have symptoms which began after the age of 6 months whose lives have been changed by the medication and whose severe symptoms have now decreased to a point where they can grow and develop with their peers, with freedom to explore and play, and without the risk of fractures, and long hospital stays.87% of respondents told us physical symptoms had improved since taking Asfotase alfa including a decreases in fractures, reduction in bone pain and fatigue and an increase in mobility. One parent told us "my child can walk unaided, her weight and height have improved and her pain levels are low now." Others told us their child is now able to participate in sport despite there being a time when he even broke his wrist just swimming. "He hasn't had a fracture since and is thriving!!" , "Strensiq has been life changing for our son. He built muscle mass that he never had, increased stamina, and he can now walk and even run up the stairs, which was once extremely heart-breaking to watch him struggle!" and "My son climbed into his own car seat today without stumbling. He climbed up the ladder on his trampoline...on his own. He kicked a ball and didn't fall down. He turned a corner, running, and didn't fall down. He danced, and didn't fall down. He laughed. He laughed a lot. He responded to me right away when I asked questions. He told grandma a joke on his iPad. He asked for food and water right when we came inside, on his own. I

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	didn't wonder what my son was thinking, feeling, or needing, for the first time in over two years. I knew without a doubt that my son wasn't in terrible pain today." Those who have grown up with having hypophosphatasia similarly tell us of the impact it has had on their lives since taking it in adulthood. There have been improvements in symptoms, alleviated pain and an ability for many to begin some form of exercise whereas previously even stepping of a curb could mean occurrence of a fracture which required orthotics and long term care. One patient told us "when I was approved for Strensiq I started with apprehension as I had been down the road to "feeling better" and nothing had worked. But after about 2 months I felt like a new person. I was pain free. My bones stopped breaking…I am literally pain free. I have my life back, my children back and I can work again." "I started strensiq. It took about 3 months but I was able to walk normal again. Eventually, I was able to work on a hospital floor. My pain is manageable and I truly believe I would be in a wheelchair right now if not for strensiq." The psychosocial impact of Asfotase alfa is vast, reducing anxiety, depression, and providing more energy and ability for self-care, socialising, and work. As a patient organisation we often hear reports of patients who have entered a downward spiral, recurring fractures alongside constant pain, joint problems, long recovery periods add to the high degree of fatigue already experienced and contribute to a decline in mental health and ability to work and socialise which further adds to feelings of depression and isolation. Asfotase alfa has helped to remove much of this and though for those with long-term symptoms there is still a need to not "over-do it" there is much more ability to manage energy levels to a point where tasks can be performed and life can resume with a real sense of hope for the future. "Strensiq has given me hope after years of rapid deterioration , my bones fracturing just doing normal every day activities ,having to have both femurs pinned due the bone weakness ,my spine deteriorating and curving ,my legs getting weaker and weaker and my mental health at crisis point . I lost my job , my husband had to retire to care for me . After one month on Strensiq I got my sanity back ,gradually over 2 years my bones have started to heal and repair ,my mobility and my ability to undertake small, tasks has gradually improved .It's a slow process and I believe that a much longer time period will be needed to see the full impact". One parent of young adults with paediatric-onset hypophosphatasia shared their perspectives about the draft guidance and the impact on their lives going forwards: "The proposed policy should consider the harm done to patients mental health if hope of effective treatment is removed…They have their whole lives to lead and HPP may limit their choice of career and how many hours they can work a week- due to reduced mobility and pain management. This generation of HPP patients - were born into a world when there was no effective treatment for HPP - now it feels like they have lost the opportunity to benefit as they are deemed too old to be entitled to treatment."
5	The current draft guidance means that those over the age of 6months will no longer have access to Asfotase alfa at the end of the agreement. There is no company agreement for this to continue and there has been no discussion about the implications for coming off medication for patients, this is a massive unknown and a huge concern for our community. All are fearful about what the future will look like and what removal of medication will mean for them or their children or people they care for. There is no awareness of the physical implications, the speed of decline, if this will be more emphasised due to already being on treatment and then it being removed, and the implication on mental health for all ages and parents/carers. For those who have already experienced the severe symptoms of hypophosphatasia removal of the medication does not bear thinking about. One patient stated that "if Strensiq is taken away from me it means any hope of leading a productive life is gone . I will cost the NHS a lot of money in other ways with multiple orthopaedic surgeries ,involvement with multiple Consultants, GP, physiotherapy, mental health services etc. The other types of intervention will not have similar outcomes for me due to the severe weakness in my bones." We were contacted by a hypophosphatasia patient in Canada who had been taking Asfotase alfa on a trial and had personal experience of treatment being declined, they told us: "I had already had numerous surgeries, femur nailing, many broken and unhealed bones, degenerating muscles and I was at the point where I felt death was more welcomed than to continue living in unbearable pain. After the year of medication, I would wonder where I had left one of my crutches as I was hobbling around on only one. The trial ended and the regression started almost immediately. It was so unfair that now the medication that was helping SO much was now denied."

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	Since the draft guidance was released we have had an increase in difficult calls with people clearly distressed about what could happen to their health in the future, people are worried and we are unable to provide any answers or much in the way of reassurances other than we are holding on to the hope that through people sharing their experiences, alongside data and insights from the company and a strong clinical perspective that the committee may be persuaded to reconsider their guidance.
6	We understand that the cost analysis of Asfotase alfa is made based on population, however we wish to emphasise that the decision to initiate treatment, as with all treatments for any condition, should be on a case by case basis by a specialist in managing hypophosphatasia in discussion with the patient, parents or carers. We do not anticipate that all paediatric-onset hypophosphatasia patients will need treatment.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology evaluation (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the evaluation consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Consultation on the evaluation consultation document – deadline for comments 5pm on 25 November 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. 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 clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Melanie Williams (Patient Expert)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Melanie Williams

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Draft guidance section 1: The MAA has been impacted by Confusing and unhelpful terminology and titling throughout the last 5 years. I am concerned about the descriptors in the MAA. The title of the Managed Access Agreement is Asfotase Alfa for treating paediatric-onset hypophosphatasia (review of HST6). In my view this is misleading because the committee has now decided to look specifically at perinatal, infantile and juvenile HPP and split the decisions accordingly. Paediatric means from 0 - 18 in the UK definition. Therefore there is potential that patients have been put into the wrong category. See document 2/8/2017: https://www.nice.org.uk/guidance/hst6/resources/contract-variation-agreement-no.-1-pdf-9254882414?fbclid=IwAR3yPYx-oDtN_NBt8PuX-nt60JUnf0rCcWjBlszvKDuOl9GAAMJEY2XU7vM The document states: Other Patients with Childhood-Onset HPP who meet the starting rules for asfotase alfa therapy include: Children aged 1-4 Children aged 5-18 Patients over the age of 18 years old with childhood-onset HPP The Scoping Document states: Six clinical forms are currently recognised: perinatal (lethal), perinatal (benign [non-lethal]), infantile (where symptoms start within 6 months after birth), childhood, adult, and odontohypophosphatasia (which only affects the teeth). Page 2, Population: People with paediatric-onset hypophosphatasia Page 4, Other Considerations: If the evidence allows the following subgroups will be considered: • People with infantile-onset hypophosphatasia People with childhood-onset hypophosphatasia. Highly confusing for clinicians, patients, committee members and Alexion.
2	Draft Guidance Section 1.2 Starting criteria Asfotase Alfa for treating paediatric-onset Hypophosphatasia published 2 August 2017: All people with perinatal- and infantile-onset hypophosphatasia, regardless of current age, can start treatment with asfotase alfa. Asfotase alfa can be considered for children (aged 1–4 years and 5–18 years) with juvenile-onset disease if they do not reach motor milestones, have pain with significant disability or have restricted mobility. The drug can also be considered for adults (18 years and over) with juvenile-onset disease if they have 2 of the following: current fractures or a history of fractures characteristic of hypophosphatasia; persistent or recurrent pain with disability; and restriction of mobility.
3	Draft Guidance Section 1.2 As patient expert to the committee you will have already read my Expert Paper together with my original letter submitted in 2017. I would encourage you to read these again. Now I should like to share my insights having been lucky enough to be a patient on Asfotase Alfa.

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	It is impossible to put this condition in a nutshell but the main issues for me pre-strensiq have been gnawing bone pain which moves around the body and in multiple places at once from severe to excruciating. Pain from chrondocalcinosis, generalised osteopenia, subchondral sclerosis, multiple sites of bursitis, tendinopathy, neuropathy, myalgia, stenosis of the spine, headaches, degenerative tendons, pseudogout, spasms in my muscles and even in my oesophagus and diaphragm. Muscle pain and weakness. I have had one non-traumatic hairline fracture in my femur. On top of this there is severe exhaustion and brain fog. Mental health issues in trying to continue dealing with the constant battle to see specialists and very limited help to manage your journey with HPP. The only medications readily available are pain killers, antidepressants and antispasmodics. The condition is progressive, multi systemic, inherited and most definitely worsens over time. I suffered bullying throughout school because I struggled to keep up with the others. I often had to lie down on the floor or needed to be carried around by my peers. It was obvious to others I was a different but because I was undiagnosed and looked 'normal' I couldn't explain why. I remember teachers calling me 'dolly daydream' because I was often distracted by being so uncomfortable. Some teachers thought I was lazy and would insist I took part in sports. I underachieved because I missed months at a time of education. These were tough times and have highly impacted my potential in life. My career has been directed by the onslaught of symptoms. I often had to leave jobs because I could no longer deal with the routines and had forced myself to match timescales until I couldn't continue. I had no diagnosis and for much of the time no access to occupational health or adaptations. My final 'employed' job ended with me being scrutinised by the occupational health team after extreme bullying by my line manager, I was forced to take time off and was finally advised to give up a job I truly loved. My only option was to become self employed so I could pace my day and purchase the equipment to be able to 'lie down' on the job when needed. I have waited for months or sometimes years to see specialists/physios but once in the system I have had the best of care from the hospitals. I have had countless cortisone injections all over my body. I have had painful shockwave therapy on my shoulders, Achilles and plantar fascia. I have had high volume injections into my Achilles heels and into my calves. I have had countless physio sessions until you reach the max allowed. The maximum sessions allowed on the NHS of acupuncture. Also numerous treatments with Ultrasound therapy. All the above time and time again. When the symptoms become so severe and you have tried all the options your only hope is an operation to try and get some relief. I have had numerous operations; on my back both shoulders twice and my elbow. Then you have deal with the recovery following the operation together with ongoing severe pain in other parts of your body. You also have to manage crutches or other aids. You have weeks or months of painful exercise to endure to regain function. This disease is systemic and relentless and there are times when you have had enough and mentally it is a huge fight to continue because you are waiting to access treatment on the NHS. It is during these periods that we have needed to pay for treatment to keep me sane or to help alleviate the symptoms of HPP whilst waiting to see specialists on the NHS. By accessing alternative therapy, osteopathy, podiatrists, physiotherapy, acupuncture, reiki, Bowen technique, aromatherapy, massage, mindfulness course, hydrotherapy and shockwave therapy you try and keep hopeful and focussed for yourself and your family. Over the 7 years we paid privately to see 2012 Shoulder specialist £200 (initial consultation) 2012 Right Shoulder arthroscopic subacroinal decompression Surgery £1500 2012 Shoulder specialist pre ESWT £200 2012 Physiotherapy 5 sessions at £35ea = £175 2012 ESWT (Shockwave treatment on left shoulder) £1000 for course of treatment. 2013 Alexander technique - 10 sessions at £35ea = £350 2014 Osteopath 5 sessions at £80ea = £400 2015 Physiotherapy 10 sessions at £40ea = £400 2016 ESWT course of treatment for plantar fasciitis and Achilles tendonitis £1000+ can't remember

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	exactly 2017 Osteopath - 10 sessions at £100ea = £1000 2018 Physiotherapy 10 sessions at £55ea = £550 2019 Physiotherapy 5 sessions at £55ea = £275 Conservative estimate of £7050 since diagnosis. Plus much dental work, crowns, extractions, bridges, root canal, x-rays - all private. It is impossible to find a dentist with knowledge of HPP you have to education your dentist and encourage them to research the disease. The costs have been astronomical over the years. I feel there is a huge burden of care from my GP practice in prescribing pain relief and mental health solutions and it has been difficult for them and for me. GP's cannot be experts in every condition, they are the ones that prescribe the pain relief and do their best in a difficult situation. You know your GP practice has done everything they can for you by prescribing and referring you to specialists. You eventually get a specialist consultation with hope and all you are offered is another operation or invasive treatment. You leave in tears - its a living hell and utterly demoralising and affects your mental health and also that of your family! It is also terrible for the consultants who have no alternatives to offer unless you can access Strensiq. This is the reality of our care pathway for HPP in the UK as adults with evidence of early onset symptoms. Now for the good news. Over the past three years I have been on Asfotase Alfa my life has changed completely. Strensiq has halted the progress of the disease at the moment. It hasn't removed all pain as I have suffered much damage prior to the medication. I have hope for the future and feel better able to cope. I haven't visited my GP for HPP over the past 3 years. My pain medication usage has reduced significantly. My anxiety and depression has also improved because I have hope that the medication will stop me breaking bones and developing other complications - I am being weaned off my medication for depression after 35 years! For the 7 years prior to starting on Asfotase Alfa I saw 50 different consultants, had 4 operations and heavily relied upon opioids, NSAIDs, antidepressants and cortisone injections. Since being on Asfotase Alfa I have only needed to visit my consultant for monitoring purposes for the review of my progress for the MAA! This evidence is compelling and life changing! My medication usage over the decades has been enormous. I have taken Omeprazole, Naproxen, Indometacin, Meloxicam, Gabapentin, Tramadol, Prednisolone, Oramorph (at different times to see if any of these helped). Cocodamol, codydramol, all for pain relief. Strivit D3 (Vit D), Escitalopram for mental health, Beta Blockers, Cetirizine (Antihistamine), Serc (for vertigo, meniere's, tinnitus). Steroid injections into joints. Buscopan for stomach problems. Antispasmodic meds Lansoprazole for spasms in my diaphragm and oesophagus muscles. I have reduced my intake of Escitalopram for my mental health from 20mg to 2.5mg and am slowly being weaned off the medication through my GP. I only take codydramol occasionally and cocodamol if I am having difficulty sleeping these days. I have clarity of mind and am no longer exhausted all the time. I have not needed painful cortisone injections into my joints during this time. I have not needed any surgery either! I have spontaneity in my life. A revelation has been my ability to drive the 300 mile round trip to visit my specialist in Sheffield unaccompanied. My husband now has more free time and is able to pursue his hobbies and adventures without worrying about me constantly. I see my metabolic specialist for monitoring visits but now I look forward to the visit. It is a great joy to be able to let her know I am doing well and that I now have an improved quality of life. You should see her smile too! Please remember there is only supportive treatment for HPP available at the moment. There have been no developments in treatments for Juvenile or Adult onset Hypophosphatasia. No other drug equals the efficacy of Strensiq at the present time. Pain and injection site reactions become insignificant compared to the benefits. My hope would be that all patients with symptoms that effect their qualitity of life would be able to

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	access AA to manage the pain, exhaustion and stop the progress of this relentless disease no matter the age of onset of symptoms. I feel the present definitions of perinatal, infantile, juvenile and adult are obsolete. It is only over the past 20 years that clinicians have been learning about HPP and as patients we are still training our doctors on how it is to live with this condition. It is still very difficult to find a hospital with knowledge of HPP in the UK and it is also a fight to get referred to a 'specialist centre'. Many clinicians are still giving a diagnosis according to how old you are when diagnosed. Therefore there are many patients who are in the wrong category and hence will be unable to access Asfotase Alfa. Letters come through from consultants and always just say Hypophosphatasia - they never state the differentiations as specified by NICE. The consultants have to see you on numerous occasions to gather your history and then make an informed decision on the age of onset of HPP. This can take a lot of time and sadly I am aware of some with HPP who have reached a point in life when they can't face any more invasive surgery or cope with the pain any longer and they commit suicide. I am 63. I have a daughter of 38 and a granddaughter of 5. We all have the same known heterozygous mutation for HPP. The genetic variants of this disease are wide. My genetics consultant stated "There is not much genotype-phenotype correlation so the fact she has a 'mild' variant doesn't mean she will have 'mild' disease. Therefore over time it seems to get back to the clinical manifestations." For my daughter, having had her first child pre-diagnosis she has now regretfully made the decision not to have any more children. If she was able to access Asfotase Alfa she most definitely would have tried for another baby in the knowledge that she would be better able to cope with the condition and also knowing that the medication would ensure future offspring would have a better quality of life. My granddaughter now just 5, with the knowledge she has HPP will have to make the agonising decision of whether to have a family or not. My daughter is finding life more and more difficult as her symptoms are developing over time. She doesn't have a social life because she is too exhausted from surviving with the condition whilst trying to earn a living. She doesn't wish to lose her home and so continues to struggle to work. She can no longer play her violin. She struggles to drive. She is following my disease pathway almost identically. But worst of all she is even struggling to hug her daughter who also is showing signs or this wretched disease! Whichever MAA classification, infantile or juvenile onset, the disease is severe and it severely effects her quality of life. She has submitted her story to the MAA. My granddaughter is 5. Her teeth have been falling out over the past few years with the roots intact. She is hyper mobile. She showed signs of bowed legs in her early months. She cries if she falls but for longer than you would expect. She gets very emotional if she injures herself. Will she follow my path too? We don't know yet. There is much evidence from across the world now showing that age of onset of this condition doesn't always interpret to NICE's strict criteria and definitions. I would appeal to you to recommend Asfotase Alfa for Juvenile onset HPP. The treatment regime is gruelling, painful and difficult to endure so patients do not take this option lightly. One thing is sure this condition is ultra rare. The treatment is miraculous and life changing. It could ensure a better future for my family and a few others in the UK who are in this lifelong struggle.
4	Draft Guidance Section 1.3 The NICE Guidance Contract 2/8/2017: https://www.nice.org.uk/guidance/hst6/resources/contract-variation-agreement-no.-1-pdf-9254882414?fbclid=IwAR3yPYx-oDtN_NBt8PuX-nt60JUnf0rCcWjBlszvKDuOl9GAAMJEY2XU7vM May have caused much confusion for Alexion to easily match the criteria as discussed in the Committee on 12th October 2022. Once again this was due to conflicting wording 'Childhood' instead of 'Juvenile'. 'Other Patients with Childhood-Onset HPP who meet the starting rules for asfotase alfa therapy

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	include: Children aged 1-4 Children aged 5-18 Patients over the age of 18 years old with childhood-onset HPP' No mention of 6-12 months at all. No mention of Juvenile but Childhood-onset HPP instead. Alexion may have difficulty answering the above because of the following: Hypophosphatasia is an ultra rare genetic condition and as such clinicians have only been beginning to diagnose the disease over the past couple of decades in the UK. As the condition is so rare it has been up to patients to work with their consultant to try and decide upon the age of onset. This is a problems for many of us with HPP. When initially diagnosed the specialist often doesn't know about the condition and they define you by the age you receive the diagnosis. Then all letters etc., that come through from consultants always just say Hypophosphatasia - they never state the differentiations as specified by NICE. The consultants have to see you on numerous occasions to gather your history and then make an informed decision on the age of onset of HPP. This can take some time and you may not have been seen by a consultant from one of the recognised centres in the UK. Equally there has been much gatekeeping by unknowledgeable consultants who have looked at the access criteria and have not fully understood the condition. They have not been referring patients to 'specialist centres'. I personally was initially diagnosed with 'Adult' onset by a local consultant. It was only after visiting a specialist centre in Sheffield that I received the correct diagnosis. I have been lucky enough to be able to access Asfotase Alfa through the MAA. Below is my evidence regarding the comparative efficacy of Asfotase Alfa and best supportive care. Over 7 years after diagnosis of HPP (9/8/2012) pre-strensiq I had 50 hospital visits to specialists which included 4 operations and other invasive treatments. The above information does not include all the privately funded visits I have made to physio, osteopaths, Mindfulness, Bowen technique, Alexander technique, etc., These visits were essential for my mental health as for each of the NHS hospital visits mentioned above you have waited for months (sometimes over a year) to see someone. In the meantime you need support just to keep positive and keep sane and try and get a bit of pain relief. On each visit your only outcome is surgery or just more bad news with nothing apart from pain relief to help without Strensiq. Since being on Strensiq 7/10/19 (3 years) - Zero visits apart from the MAA monitoring visits. I have not had to visit my GP practice once for my HPP since beginning on Strensiq. There is only supportive treatment for HPP available at the moment. There have been no developments in treatments for Juvenile or Adult onset Hypophosphatasia. No other drug equals the efficacy of Strensiq at the present time.

Insert extra rows as needed

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- Complete the disclosure about links with, or funding from, the tobacco industry.
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User	Consultation Name	Document Name	Chapter Name	Section Header	Section Number	Selected Text	Comment	Question Text	Yes/No Answer	Answer Text	Represents An Organisation	Organisation	Has Tobacco Links	Tobacco Link Details
Responde 1	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)	recommendations	1 Recommendations	1.2		Juvenile and infantile onset can be very similar in presentation and only vary in the age by weeks or months. Considering the rarity of the condition, delays in diagnosis in the infantile presentation can result in being diagnosed as Juvenile				No		No	
Responde 1	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)	committee-discussion	Population in the decision problem and clinical efficacy evidence	3.6		Clinical status rather than age at onset would reflect the difficulty of diagnosing these patients				No		No	

				provided											

Resondee 5	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)					I have Hypophosphatasia ,I am on Strensiq . I would like the committee to consider that this decision ,excluding people with a juvenile hypophosphatasia diagnosis from accessing Strensiq treatment ,could mean discrimination against people diagnosed as adults ,particular those in older middle age whose symptoms were consistently not recognised by doctors as hypophosphatasia when they were babies and whose medical records are often sparse or unavailable due to the nature of recordkeeping at the time. Evidencing issues that occurred in the early 1960s when pregnant women didn't even have routine ultrasound scans is very difficult and therefore may prejudice people being able to give a full account of their very early issues . This group of people no matter how severe their current symptoms would be excluded from treatment , whereas younger people who have now have access to far superior screening during pregnancy and monitoring as young children may have less need for the treatment but will still be able to access it if needed . If you do restrict the access to treatment further(you already have to be severely affected to qualify) ,please still consider having a route for people devastated by this condition but who do not tick the right boxes to make a case for treatment , they may well be costing the NHS a great deal in other respects .				No		No	

Respondee 2	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)	committee-discussion	3 Committee discussion	3.20	Other factorsComment on section: Equality issuesEquality issuesComment on subsection: 3.21 3.21	The committee discussed the issue of age, and outlined they identified 'no other potential equality issues'. We request the committee address that there is not geographically equitable access for infants and children to Hypophosphatasia treatment across England, due to the current NHSE commissioning arrangements. There are currently only 3 Paediatric Hypophosphatasia treatment Centres, and they are clustered at similar latitudes in Mid-North England. Infants and children in South West England and the South East England incur long travel journeys (8-12 hours round trip, 300-500 miles) which represents a large emotional, practical and financial burden on families, including parents and siblings. This burden can be protracted throughout the long patient treatment journey, particularly during initial extended neonatal inpatient admission (often 3-6 months). This impact compounds burdens when families have additional health needs and disabilities in other family members – a situation currently experienced. There are centres each in the South West and the South East with expertise in hypophosphatasia management and comprehensive tertiary multidisciplinary services to undertake Hypophosphatasia treatment in order to provide treatment closer to home and lessen the burden on the families. We request the committee give this equity of access due consideration in their deliberations				Yes	University Hospitals Bristol and Weston NHS Foundation Trust	No	

							as to how this treatment can be most appropriately arranged.							

Responde 3	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)	recommendations		1		The trial was interrupted by the Covid pandemic - that will have reduced recruitment of new patients to the trial. The trial for juvenille onset HPP patients should be extended by a further 2 years to Dec 2024. Not enough research is available re effectiveness of Asfotase alfa for patients with juvenille on-set HPP - the Strensiq trial should be extended to include a wider set of juvenille on-set HPP patients to confirm if Strensiq is effective at reducing pain, improving bone strength and healing stress fractures that don't heal on their own for HPP patients and preventing future reqs for expensive surgery to insert plates or pin fractures. Both my daughters now aged 22 and 24 have juvenille on-set HPP and they will likely benefit from Strensiq treatment to improve their mobility, allow them to work full-time and live a full life. Without Strensiq each daughter has required expensive surgery and hospitalisation to fix fractures - 3 operations in total across the two girls at ages of 2, 5 and 13. It is unfair to stop the Strensiq trial now - it should be extended for juvenille on-set HPP - with a future review point. HPP is highly variable - so medical specialists should be able to prescribe Strensiq on a case-by-case basis depending on severity of symptoms each patient exhibits and the potential benefits which are specific to each patient. HPP symptoms don't neatly fit to a general standard classification.				No		No	

Respondee 3	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)	recommendations	1 Recommendations	1.1		HPP symptoms are highly variable - I don't agree that age of onset is a reliable determinant of HPP prognosis or severity of future symptoms. It would be better to provide some flexibility to clinicians on a case-by-case basis when dealing with juvenille onset HPP patients - granting them flexibility to prescribe Asfotase alfa to those patients with severe symptoms of reduced mobility and pain that would be effectively treated and managed by Asfotase alfa. There is a strong economic case for those patients of working age that Asfotase alfa treatment will extend their working life which otherwise will be restricted - this should be considered in the cost-benefit economic evaluation for juvenille onset HPP patients				No		No	

Responde 3	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)	recommendations	1 Recommendations	1.3		This further clarification and trial for juvenille on-set HPP should be extended by 2 years due to impact of the Covid pandemic. Dec 2022 is to soon to collect this data and do sensible analysis - it should be extended to a further review point in Dec 2024 and Strensiq should still be available to juvenille onset patients during this trial extension . The Asfotase alfa trial was interrupted by the Covid pandemic - many NHS services were stopped. My daughter was referred to specialist waiting list with leg pain and reduced mobility in 2019 but due to the pressure on the NHS during the pandemic she was not approved to start a Strensiq trial until Oct 2022. Many NHS out patient services were cancelled during the pandemic and patients were deprived access to the trial and waiting lists got longer. It is unfair to propose an end to the trial now before there is enough evidence of the effectiveness for juvenille on-set HPP patients. This is especially true for Scotland which will typically follow the NICE advice and guidelines - but where there have been known blockers and challenges to the start of the Strensiq trials in Scotland. Please publish how many patients in Scotland have been included in the Asfotase alfa trial to date. There has been a post-code lottery in terms of access to the Asfotase alfa treatment. My other daughter might in future benefit from Strensiq treatment - as HPP symptoms are highly variable - prescription should be on a case-by-case basis				No		No	

							based on clinical judgement by a specialist clinician								

Responde 3	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)	committee-discussion	Cost-effectiveness estimates in juvenile-onset hypophosphatasia	3.19		Trial and study should be extended by 2 years to Dec 2024 given the impact and disruption of the Covid pandemic, and the resulting uncertainty on the juvenille-onset HPP data, as not enough data has been collected to date. During this extended trial period - Strensiq should still be available for juvenille onset HPP patients.				No		No	
Responde 3	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)	committee-discussion	Recommendations	3.23		Trial and study should be extended by 2 years to Dec 2024 for juvenille-onset HPP, given the impact and disruption of the Covid pandemic. Trial needs to be extended to reduce uncertainty of the juvenille-onset HPP data, as not enough data has been collected to date. During this extended trial period - Strensiq should still be available for juvenille onset HPP patients.				No		No	

Resondee 4	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)					Please take note of my comments as a person living with symptoms since early childhood. This is a short summary of the burden of this disease and the impact on my daily life I am finding it more and more difficult to cope and really need help to control the pain. Some days I struggle to take my coat on and off. Sometimes I need help to get out of the bath. Help out of chairs or getting out of the car. Struggling opening big doors or holding doors open for people. Holding/cuddling/playing with my little girl. Playing my violin. Holding my phone while talking to someone for a long period of time (my arm will seize up). Keeping up with house work. I often feel restricted and helpless and sometimes can only sit with heat pads until the pain eases a little. Unable to shop due to difficulties pushing the trolley and handling all the shopping. Inability to continue with past hobbies or joining in with friends - you lose your sociability as you have to consider how you are going to cope with the day after. Extreme discomfort trying to work in an environment that is not tailored to your needs. Not able to fulfil your role easily in the job you have been employed to do - leading to frustration, depression and anxiety as you struggle to continue! Having to go to bed early or sleeping during the				No		No	

							day and not doing much at weekends so that I can rest and catch up from the week before. Being unreliable to friends and family as I don't know how I am going to be. I am a very wriggly person, as I cannot stay in one place for long, due to feeling uncomfortable (this has always been the case). Dealing with the unknown, what is going to happen to me, will I lose my independence? Will I have to have a wheelchair? Will I need help at home? Coping with my anxiety and depression due to all of these burdens. Constant worrying about the people around you and the burden you put on them, even though they would never say this themselves. Asfotase Alfa (Strensiq) is my hope. It is a chance for me to improve my quality of life, continue working and not be a burden on my family, friends and the NHS.							

Respondee 4	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)	recommendations	1 Recommendations	1.3		'Comparative efficacy analysis of asfotase alfa and best supportive care in people with juvenile-onset hypophosphatasia for all relevant outcomes' - There is no 'supportive care' that compares with Asfotase Alfa. The only other option is visiting consultants and waiting for appointments. Discussing pain management with different doctors who won't know much about HPP if they even know about it at all.				No		No	
Respondee 4	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)	recommendations	1 Recommendations	1.4		If treatment will cease for those patients who have been fortunate enough to access Strensiq - what will happen to these patients? Will there be counselling? Back to taking high doses of pain killers? Going back on to antidepressants to cope with the pain - but also the trauma of having to come off Strensiq? Suicidal thoughts/feelings - and in the worst case scenario - suicide?				No		No	
Respondee 4	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)	recommendations	1 Recommendations	1.4	Paediatric-onset hypophosphatasia is a rare genetic condition that affects the way calcium and	Paediatric-onset hypophosphatasia - here you are using the words 'paediatric-onset' however NICE have decided to put these into sub-categories. Perinatal, infantile and juvenile. Paediatric is referenced in other places in the document. When this happens do you mean all three sub-categories? i.e. 2.1, 3.4				No		No	

						phosphorous are deposited in developing bones and teeth. There are limited treatment options and it can substantially affect the lives of people with the condition, their families and carers.									

Resondee 4	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)	committee-discussion	Paediatric-onset hypophosphatasia	3.1	Juvenile-onset hypophosphatasia that develops later in childhood has a substantially lower mortality rate.	Of course, saving lives of babies with perinatal or infantile onset is important - but what about the quality of life of those who have juvenile onset. Many people with juvenile onset that develops later in childhood are still severely affected with pain, mobility issues, headaches and mental health. What about the mortality of those who will not be able to access this life changing medication?				No		No	
Resondee 4	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)	committee-discussion	Data sources	3.4	paediatric-onset hypophosphatasia	paediatric? Perinatal, infantile or juvenile?				No		No	
Resondee 4	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia	committee-discussion	Data sources	3.4	paediatric-onset hypophosphatasia	paediatric? What do you mean by this? Paediatric means from 6 months to 17 according to your NICE definition. Its not clear which form you are referring to i.e., Perinatal, infantile or juvenile?				No		No	

		(review of HST6)													
Resondee 4	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)	committee-discussion	Data sources	3.4	paediatric-onset hypophosphatasia	''The traditional clinical description of HPP is based on categorising the disease by age of onset:'' Perinatal, infantile and juvenile. In 3.4 you discuss evidence using the term 'paediatric' - not Perinatal, infantile or juvenile. Why has this not been cut up into categories?				No		No	
Respondee 5	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)					Hypophosphatasia is a rare genetic disorder with variable severity. The impact of therapy on patients with perinatal or infantile HPP is clear. My comments are restricted to application of HST 6 to adults.				No		No	
Respondee 5	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia	committee-discussion	Source of utility values	3.13		It is not clear within the MAA for adults on HPP, how the EQ5D utility scores for 9 patients in severity level 1 and 2 differed from the vignette.				No		No	

		(review of HST6)												
Responde 5	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)	committee-discussion	Carer disutility	3.14	It recognised that events such as seizures, which have a profound impact on carers, are more common in hypophosphatasia.	The carer utility for adults with juvenile onset HPP is not clearly stated where fits are not common.				No		No	
Responde 5	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)	committee-discussion	Asfotase alfa cost	3.15		The current cost is weight-based. There is a wide variation in annual cost between those weighing 50 kg and 100kg. Taking an average weight may mask a benefit if the average weight is higher with wide variability. There should be a ceiling annual cost for adult treatment irrespective of weight to simplify the model.				No		No	

Responde 5	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)	committee-discussion	Cost-effectiveness estimates in juvenile-onset hypophosphatasia	3.20	Present subgroup analyses of data specific to people with juvenile-onset hypophosphatasia based on data collected during the managed access agreement, the asfotase alfa clinical trial programme and from the global registry for all relevant	Adults with juvenile onset have a very variable phenotype that would be expected to be less severe than those with perinatal or infantile HPP. One adult phenotype in juvenile onset HPP is severe chronic pain and severe fatigue unrelated to fractures. There is also subset of adults with juvenile onset HPP with recurrent disabling long bone fractures. These subgroups of adults would be expected to have a different time to onset and scale of benefit from therapy. At present the approach seems to be to combine these varied groups into a single composite of severely affected cohort. For example a slow 6MWT maybe due to pain and disability from unhealed fractures vs. widespread pain and fatigue. This may mask a clear benefit within a specific adult sub-group.				No		No	

						outcomes (see section 3.5).									
Responde 5	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)	committee-discussion	Uncaptured benefits	3.22		It is not clear from the MAA if productivity losses have been reduced.				No		No		

Responde 6	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)					Comments from Dr Katie Moss FRCP 1. Clinical experience of treating adults with asfotase alfa I am a rheumatologist working at one of the Specialist centres for adults with hypophosphatasia. I have treated 11 patients with juvenile onset hypophosphatasia with asfotase alfa under the MAA. It is clear to me that these patients carry a high health burden, with 4 patients being unable to work and the other 7 patients working reduced hours/other work adjustments due to having hypophosphatasia. In my experience, the health burden is similar or worse that the health burden of rheumatoid arthritis, for which there are several NICE approved treatments. My experience is that the patients I have treated have benefitted greatly from asfotase alfa. In my experience, this treatment in adults reduces pain and fatigue and improves mobility, ascending stairs is easier, likely due to an improvement in muscle weakness. Patients are able to do more (and participate more easily in social activities such as meeting friends), have a better quality of life and there is a benefit of improved mood. One patient has reported less days of work due to sickness and 2 patients have been able to increase their working hours due to health improvements since starting treatment. However, none of these 11 patients were diagnosed within the first 6 months of life, so they would all be excluded from treatment if the				No		No	

							draft NICE guidelines are accepted. Below I describe outcomes for 3 patients treated with asfotase alfa which illustrate the benefit I have witnessed of this treatment in adults (who would be excluded by the draft guidelines criteria) Patient 1 was diagnosed at age 3, therefore he would not qualify under the proposed treatment cut off of 6 months. In childhood he had leg pain, prominent fontanelles in the skull, tooth loss and short stature. At age 3 he was diagnosed with severe hypophosphatasia and he has had multiple health problems since then including: 4 operations on Skull/neurosurgery for skull base deformity/foramen magnum decompression; multiple delayed union of metatarsal foot fractures; bilateral femoral fractures, one of which did not heal – non-union after 2 years, despite surgery. He had to walk with 2 crutches. Since asfotase alfa, this fracture has healed, he reports more energy and he feels stronger, his mobility and quality of life has improved considerably. He clearly has severe hypophosphatasia, as demonstrated by multiple recurrent slow healing fractures and skull deformity, yet I am concerned that he would be excluded from asfotase alfa treatment due to being diagnosed at age 3. Patient 2 has severe hypophosphatasia diagnosed at age 7 and she had to stop working in her 40's due to pain and disability. One of her many symptoms was episodes of severe hip pain at rest and night pain unrelieved by analgesics.							

							During these flare ups, she would be unable to walk for 2-3 weeks, and this happened every 8 weeks, so this affected her life considerably. Since commencing asfotase alfa, these pain flare ups have resolved. This patient was diagnosed with hypophosphatasia at age 7, so she would be excluded from treatment if the draft NICE guidance is accepted. Patient 3 was diagnosed with hypophosphatasia at age 50. She has short stature and severe musculoskeletal pain, she has had more than 20 spinal procedures/operations and has been unable to work since age 40. Since early childhood, for as long as she can remember, she has had leg pain (long bone pain) which is severe and relentless and interrupts her sleep. Since started asfotase alfa, the long bone pain in her legs resolved. She was diagnosed with hypophosphatasia at age 50, so she would not qualify for treatment under the draft guidance. In my experience, asfotase alfa has had a very significant benefit when started in adults with juvenile onset hypophosphatasia. None of my patients were diagnosed before age 6 months, so they would all be excluded from this licensed enzyme replacement therapy if the draft guideline was implemented. I am concerned that they will be excluded due to age and this could be considered as discriminatory. 2. Diagnostic delay is common in hypophosphatasia A long diagnostic delay is well documented for							

							hypophosphatasia (diagnostic delay of 10 years shown in the Registry study) and there is evidence that symptoms can progress over time, I do not think is acceptable to exclude patients diagnosed after 6 months from this effective treatment. 3. Comparison of patients treated with asfotase alfa under the MAA with patients enrolled in the Registry study I do have concerns about comparing the treated patients in the Managed Access Agreement to patients enrolled in the Registry study (ALX-HPP-501), because the severity of hypophosphatasia in these 2 cohorts is not comparable. To my knowledge, all patients with severe hypophosphatasia in England, were referred for asfotase alfa and most started asfotase alfa treatment. Therefore the other patients in England enrolled in the Registry study will almost all have less severe disease. Registry study patients from other countries (not England), who may not have been treated, may not be comparable in other ways (such as different healthcare standards).							

Responde 7	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)					I think the appropriate response to this guidance it for you to see the 'before' and 'after' effect of Asfotase alfa in a (consented) patient. This patient would be *made ineligible* for treatment by the new ID3927 guidelines. This is because she presented after 6 months of age. She has particularly severe hypophosphatasia (both allelles affected) and presented with multiple fractures of the lower limbs and ribs. Please revise the guidelines to permit ongoing usage for patients with severe hypophosphatasia disease who stand to have a life-changing response- in this case going from the use of a wheelchair to aid-free ambulation. Effect of asfotase alfa : Severe hypophosphatasia, onset as child, attempt at 6 minute walk test for asfotase eligibility https://www.dropbox.com/s/us8p0x8e7wwn8a4/Hypophosphatasia_pre_treatment290819.wmv?dl=0 *After asfotase* treatment video of 6 minute walk test: https://www.dropbox.com/s/2e2w48z7t1ldfv8/Asfotase_effect_post_treatment130520.wmv?dl=0				No		No	

							From:**********Sent: 21 November 2022 14:47 To: ********** Subject: Re: NICE re-evaluation of asfotase alfa - urgent update Dear Liz I thank you for the telephone conversation re: videos of myself. I hereby give my full permission the use of any videos relating to myself that can be used as evidence of how effective the drug is. I am extremely concerned that NICE may be considering declining the treatment and would let NICE see me in person and ask me questions and how this treatment has transformed my life and my family, also if you need me to do any updates on the videos. Look forward to seeing you on Wednesday and can discuss it more then. Best regards							

Responde 9	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)	recommendations	1 Recommendations	1.2		HPP is a progressive and degenerative disease. Leaving people without treatment means they will get worse and require various surgeries and options to manage. Degeneration is not reversable.				No		No		
Responde 9	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)	recommendations	1 Recommendations	1.4	Asfotase alfa has not been compared with best supportive care in this population.	Supportive care options by the NHS is extremely limited and inadequate. Many patients are having to watch their bodies deteriorate in front of their eyes. Pain management is non existent. Pain killers make little difference- suicidal thoughts can occur from the constant agony of living with this condition. Mental health issues have been missed from this document. Extreme anxiety and/or depression can occur quickly due to the complete uncertainty of how the disease will progress and the lack of support individuals may have.				No		No		
Responde 9	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)	committee-discussion	Effects on quality of life	3.2	needed off work to attend appointments.	If those had been treated with AA at time of first symptoms and not waited the long periods between Managed Access and other factors, the drug could prevent/slow down the degeneration. Without the drug many will have to stop working and rely on disability care. Symptoms can deteriorate very quickly. Waiting a year can make a HUGE difference.				No		No		

Responde 9	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)	committee-discussion	Cost-effectiveness estimates in juvenile-onset hypophosphatasia	3.20		You are preventing access to a drug which can stop degeneration (or at least slow it down). Why are you playing with people's health? What are we waiting for? We know the disease will get worse, so why are we leaving patients without help or means? There is no other treatment that can slow down or prevent degeneration- patients are being left in unimaginable pain and mobility issues.				No		No	
Responde 9	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)	committee-discussion	Recommendations	3.23		Most HPP patients will be paying out of pocket/ through private health care to support their condition. I personally have spent thousands and thousands of pounds each year to fund my illness. The wait time and support from the NHS can be slow at times, so often patients will have to fund surgeries/ physio/ medication entirely themselves. Therefore, the NHS will be seeing only a small portion of drug and value of money. Also, if individuals have to stop working, they will need to claim disability and will not be contributing to society in the same way.				No		No	

Responde 8	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)					The recommendations exclude one (consented) patient whose bone mineralization I have studied as a research scientist. Asphotase Alfa has had a dramatic (and predictable) improvement on this patient's health and quality of life. Prior to treatment she suffered almost constant fractures which typically were very slow to heal. Consequently, she spent most of her recent life before Asphotase Alfa treatment using a wheelchair. I led a research team to investigate the molecular structure, composition and distribution of mineral in bone biopsy samples from this patient (under full consent and appropriate ethical guidance). In the 20+ years that I have been studying the molecular structure of bone mineral, I have never seen such aberrant bone mineral structure or organization of the mineral crystals. That the patient suffered frequent fractures was absolutely no surprise. This degree of aberration in bone mineral structure could potentially be expected to affect calcium homeostasis in this patient and ultimately lead to further pathologies. Although this patient had juvenile onset of hypophosphatasia symptoms, they were first recorded after the age of 6 months. She would therefore be excluded from continuing treatment under the guidance being recommended in this report. It is very clear from "before" and "after" videos of this patient that Asfotase Alfa has led to a truly dramatic improvement in her ability to walk - from almost non-existent to close to normal. I				No		No	

							would be concerned for this patient's health even beyond her bone health and pain level if her treatment were to be stopped. Undoubtedly, her bone mineral would revert to the pre-treatment composition and structure, with frequent fractures likely to present, but I would also be seriously concerned about whole-body calcium homostasis and further pathologies arising from dysfunctional calcium homeostasis.							

Respondee 10	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)	committee-discussion	Effects on quality of life	3.2		Whilst this is highly relevant to children with HPP it seems to gloss over the particular issues in adults whose disease deteriorates in middle life. Please see more detailed comment below regarding end points				No		No	

Respondee 10	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)	committee-discussion	Data sources	3.4		Whilst this data may be the best that is available in terms of trial evidence this does not represent the majority of patients who I see in a specialised adult metabolic bone clinic. There is clear clinical progression of symptoms with age and in many patients who had evidence of paediatric onset primarily on account of early loss of deciduous teeth the bone disease does not become clinically manifest until middle life with the onset of crippling bone pain and multiple fractures. I fear that the committee may not have been given the opportunity to have a true understanding of the nature and extent of disease burden in this population as I do not really see a description of the sort of patient I see in my clinic whose life is blighted by bone pain and fractures. Whilst many of the outcomes listed in this section are absolutely appropriate for children with HPP the vast majority of these are completely irrelevant for adults. For my patients the only really relevant endpoints are pain, fractures, adverse effects and HRQOL. I am not even sure that mortality is relevant as most of my patients will die with HPP rather than from it. Overall survival and ventilator free survival are of no comparative use in the adult population				No		No	

Responde 10	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)	committee-discussion	Categorisation of population	3.5		This section fails to do justice to the pattern of disease in adults with paediatric onset whose symptoms deteriorate in middle life.				No		No		
Responde 10	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)	committee-discussion	Comparative analysis based on survival outcomes	3.7		This section does not appear to address comparisons in adults with paediatric onset HPP. The comparisons using mortality and respiratory outcomes are not relevant to this population.				No		No		
Responde 10	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)	committee-discussion	Changes in best supportive care	3.8		I am not aware of similar time related changes in BSC for adults with HPP				No		No		

Responde 10	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)	committee-discussion	Cost-effectiveness estimates in juvenile-onset hypophosphatasia	3.20		I accept the paucity of data for adults and welcome the questions raised by the committee. However I am concerned that this is still requesting data on what amount to irrelevant end points for the patient population I deal with. Juvenile onset HPP in a teenage population is very different from the manifestations of the same condition in a population in middle to later life				No		No	
Responde 11	Evaluation consultation	Asfotase alfa for treating paediatric-onset hypophosphatasia (review of HST6)					Some adults present later than these guidelines suggest, but still benefit from asfotase alfa treatment. I work in a tertiary met bone centre with personal experience of such a patient whose quality of life was transformed by this treatment. This revised guidance would have denied this patient this option. I would recommend allowing treatment in adults in tertiary referral centres in selected circumstances.				No		No	