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1 March 2017

APPEAL AGAINST THE FINAL EVALUATION DETERMINATION FOR SEBELIPASE ALFA FOR THE TREATMENT OF LYSOSOMAL ACID LIPASE DEFICIENCY

EXECUTIVE SUMMARY

Alexion's appeal against the Final Evaluation Document for sebelipase alfa for the treatment of lysosomal acid deficiency (LAL deficiency) is based on the following grounds:

Ground 1

- The failure to follow a clearly defined procedure in this HST evaluation is conspicuously unfair and is the direct cause of the unfavourable aspects of the proposed guidance
- There has been no effective consultation on the proposed recommendations for sebelipase alfa in the context of the managed access agreement
- The Committee's assessment of value for money is unfair and fails to consider the population of patients eligible for treatment within the managed access agreement
- The Committee has provided no adequate reasons for its conclusions regarding the determination of the population of patients eligible for treatment within the proposed managed access agreement for sebelipase alfa
- The Committee has failed adequately to take into account the benefits of sebelipase alfa in infants with rapidly progressing lysosomal acid lipase deficiency
- The exclusion of a clinical expert from the meeting of the Evaluation Committee in November 2016 was unfair and is likely to have prejudiced this evaluation
- The Committee has provided no reasons to justify its criticisms of the trial data for use of sebelipase alfa in babies presenting before 6 months
- The Committee has failed to consider the status of children with juvenile-onset LAL deficiency in accordance with the provisions of the Human Rights Act 1998
- In reaching its conclusions regarding sebelipase alfa, the Committee has failed to take into account relevant evidence

Ground 2

- The Committee's criticism of Alexion for failing to incorporate collection of non-invasive measures of liver damage in the proposed managed access agreement are unreasonable in circumstances where such measures have not been validated in LAL deficiency
- The Committee's explanation for preferring the utility values selected by the Evidence Review Group does not justify the values selected

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INTRODUCTION

Sebelipase alfa (Kanuma®) is a recombinant human lysosomal acid lipase (rhLAL), which is indicated for long-term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase (LAL) deficiency. It is the only specific treatment for patients with LAL Deficiency and has been shown in clinical studies to produce significant improvements in serum transaminases, disease-related lipid abnormalities, and liver fat fraction in children and adults and improvements in survival and growth in infants

Sebelipase alfa was granted a marketing authorisation by the European Commission under the centralised procedure on 28 August 2015 following a positive opinion issued by the Committee for Medicinal Products for Human Use (CHMP) issued on 25 June 2015. The product was assessed under accelerated assessment due to the lack of effective treatment and the high mortality of the disease in infants.

Sebelipase alfa is indicated for long-term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase (LAL) deficiency.

PROCEDURAL HISTORY OF THE EVALUATION

Below is a summary of the history of the NICE HST evaluation for sebelipase alfa.

May 2013	**Interim Process Guide for Highly Specialised Technology (HST) Evaluations** Described as an "outline process"
June 2015	**Sebelipase alfa referred for HST evaluation by NICE**
August 2015	Final Scope for HST evaluation of sebelipase alfa
19 August 2015	NICE notifies Alexion verbally that there is a possibility that NICE might introduce managed access agreements (MAAs) into the HST procedure, as a methodology to address the challenges of HST evaluations and the high costs of such technologies. Alexion is informed that NICE is, at that time, preparing a draft template and this would be sent to us in due course. Alexion was not notified during this discussion that MAAs were a requirement of the HST procedure and NICE has at no time published any guidance in relation to the structure and content of a MAA, how this should be prepared or addressing the involvement of the various stakeholders in this process.
3 September 2015	Outline template for MAA (headings only) provided by NICE to Alexion

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14 October 2015	Submission to NICE by Alexion in relation to sebelipase alfa for the treatment of lysosomal acid lipase deficiency
3 December 2015	Alexion submits proposed patient access scheme (PAS) to the Department of Health and to PASLU
20 January 2016	**First meeting of the Evaluation Committee to consider sebelipase alfa**
11 February 2016 - 10 March 2016	**Consultation on first Evaluation Consultation Document (ECD)** **"1.1 Sebelipase alfa is not recommended for treating lysosomal acid lipase (LAL) deficiency in people who presented with rapidly progressive LAL deficiency before they were 6 months old except as part of a clinical trial.** **1.2 Research should be designed to generate robust evidence about the benefits of long-term treatment with sebelipase alfa compared with shorter-term treatment with sebelipase alfa ('bridging therapy') followed by haematopoietic stem cell transplant with curative intent.** **1.3 Sebelipase alfa is not recommended for treating LAL deficiency in people who did not present with rapidly progressive LAL deficiency before they were 6 months old".** Responses to consultation include a draft managed access agreement (MAA prepared by Alexion following preliminary discussions with clinical experts and patient organisations
22 March 2016	**Second meeting of the Evaluation Committee to consider sebelipase alfa**
7 April 2016	Letter from NICE to Alexion providing feedback from the HST Evaluation Committee in relation to the draft MAA submitted by Alexion for the purposes of another HST evaluation (asfotase alfa). In relation to general guidance, the letter stated that only one MAA had been put in place at that stage and "that there is no set expectation of what should be contained within such an agreement". Each MAA "should be developed using the MAA format and headings that have been used for the previous evaluation and with the HST Committee's decision-making criteria in mind (as described in the Interim methods and process statements). It is imperative that the MAA does not focus solely on the clinical criteria relating to the nature of the condition and impacts of the technology etc. It should also consider aspects that mitigate financial risk

	to the NHS and PSS including overall cost." Specific comments in relation to asfotase alfa stated that stakeholders should identify in the MAA the patients who would be expected to benefit most from treatment. Subsequent telephone call with when she stated that Alexion should follow the same approach for sebelipase alfa.
26 April 2016 - 25 May 2016	**Consultation on second ECD** **"1.1 Sebelipase alfa is a potentially life-saving treatment for babies with rapidly progressive LAL deficiency, and there is a compelling clinical need. However, the committee was unable to reach a conclusion on the value for money offered by the company's managed access proposal because no associated estimates of costs and benefits were supplied by the company.** **1.2 The committee is therefore minded not to recommend sebelipase alfa for treating lysosomal acid lipase deficiency. The committee recommends that NICE requests further clarification from the company, which should include:** • **updated budget impact and cost–consequence analyses using the list price to show the impact of the committee's preferred cost–consequence and budget impact modelling assumptions** • **updated budget impact and cost consequence analyses to show the impact of the managed access proposal including the committee's preferred cost–consequence and budget impact modelling assumptions, and any financial arrangements that would reduce the cost to the NHS** • **separate budget impact and cost–consequence analyses for each patient group if the managed access proposal has different criteria for different patient groups".** Responses to consultation include a revised MAA prepared by clinical experts, patient organisations, NHS England and Alexion.
20 July 2016	**Third meeting of the Evaluation Committee to consider sebelipase alfa**

21 July 2016	PASLU Expert Panel meeting to approve advice for PAS for sebelipase alfa. Following this meeting, Alexion was invited to submit additional information regarding the PAS. This was provided to PASLU in early August 2016. However Alexion has received no further information or communication regarding the PAS. In particular there has been no communication from PASLU or the Department of Health refusing or approving the PAS.
7 October 2016	Alexion is informed that, despite earlier assurances that a further ECD would be issued, NICE proposes to publish a Final Evaluation Document (FED). Ultimately, following submissions by Alexion, this decision was reversed.
18 October 2016	Alexion submits updated clinical trial results and a commercial proposal to NICE.
22 November 2016	**Fourth meeting of the Evaluation Committee to consider sebelipase alfa**
8 February 2017	**Final Evaluation Determination (FED) is issued to consultees:** **"1.1 Sebelipase alfa is not recommended for long-term enzyme replacement therapy for treating lysosomal acid lipase (LAL) deficiency in babies with rapidly progressive disease. The committee recognised that sebelipase alfa is potentially life-saving in this population and there is compelling clinical need. It was concerned that, even with the company's proposed discount and cost cap, the cost of sebelipase alfa is exceptionally high and too high to be considered value for money in the context of uncertainties about the potential long-term benefits of treatment.** **1.2 Sebelipase alfa is not recommended for treating LAL deficiency in children or adults."**

LYSOSOMAL ACID LIPASE DEFICIENCY: BACKGROUND INFORMATION

Lysosomal acid lipase (LAL) deficiency and its treatment is considered in detail in Alexion's original Submission to NICE for the purposes of this evaluation, dated 14 October 2015. In this Appeal Letter, we provide a brief summary, as background information to assist the Panel. This summary does not, however, replace the more detailed information submitted earlier in the HST evaluation process.

LAL deficiency is an ultra-rare, inherited, autosomal recessive disorder, where the relevant genetic

mutations lead to a decrease or loss of LAL enzyme activity. Affected individuals therefore experience a build-up of fats within the cells of vital organs, blood vessels, and other tissue (Grabowski (2012)[1]). In the liver, LAL deficiency leads to hepatomegaly, steatosis, fibrosis, cirrhosis, and often progresses to liver failure requiring a liver transplant at an early age. LAL deficiency also results in accelerated atherosclerosis, that contributes to morbidity and mortality in the broader LAL deficiency population (Bernstein (2013)[2]; Burton (2015)[3]) and other devastating systemic complications, including splenomegaly, anaemia, and thrombocytopenia. An estimated 87% of LAL deficiency patients experience manifestations of disease in more than one organ (Bernstein (2013)[4]).

The disease may present during infancy (around 2 to 4 months of age), when it is rapidly progressive and generally results in death within the first year of life. Infants with LAL deficiency represent a medical emergency as they experience a rapidly progressive condition characterised by malabsorption, growth failure, and liver failure with the median age of death 3.7 months (Jones (2015a)[5]). In other patients, the condition presents in early childhood or in adults, when life expectancy is dependent on the severity of the disease and associated complications. The median age at first onset in children and adults is 5 years of age, with 83% presenting at 12 years of age or younger (Bernstein (2013)[6]). It is estimated that approximately 50% of children and adults with LAL Deficiency progressed to fibrosis, cirrhosis, and liver transplant within 3 years from clinical manifestation onset (Data on File, CSR LAL-2-NH01).

Treatment with sebelipase alfa and replacement of LAL enzyme activity leads to reductions in liver fat content and transaminases, and enables metabolism of cholesteryl esters and triglycerides in the lysosome, leading to reductions in low-density lipoprotein (LDL) cholesterol and non-high-density lipoprotein (HDL) cholesterol, triglycerides, and increases in HDL cholesterol. Improvement in growth occurs as a result of substrate reduction in the intestine. Clinical trial data have shown that in the first cohort of infants studied, 5 out of 9 infants treated have survived beyond 3 years of age, with the oldest now 6 years of age and attending school. These children have not only survived, but have achieved normal developmental milestones.

GROUNDS OF APPEAL

1. GROUND 1: IN MAKING THE ASSESSMENT THAT PRECEDED THE RECOMMENDATION, NICE HAS a) FAILED TO ACT FAIRLY OR b) EXCEEDED ITS POWERS

[1] Grabowski, GA. The Wolman disease / cholesteryl ester storage disease spectrum. The Online Metabolic and Molecular Basis of Inherited Disease. 2012; 142.
[2] Bernstein D et al. Cholesteryl ester storage disease: review of the findings in 135 reported patients with an underdiagnosed disease. J Hepatol. European Association for the Study of the Liver; 2013;58(6):1230–43
[3] Burton BK et al. Clinical Features of Lysosomal Acid Lipase Deficiency − a Longitudinal Assessment of 48 Children and Adults. 2015; 61(6): 619–625.
[4] Ibid
[5] Jones S et al. Enzyme replacement with recombinant human lysosomal acid lipase (rhLAL) in patients with cholesteryl ester storage disease, the late onset form of LAL deficiency, produces sustained decreases in transaminases and reduction in liver fat content. 63rd Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2012 Boston, MA United States. Hepatology 2012a; 56: 824A-825A
[6] Ibid

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1.1. The failure to follow a clearly defined procedure in this HST evaluation is conspicuously unfair and is the direct cause of the unfavourable aspects of the proposed guidance

Background: requirement for a defined process

It is a fundamental aspect of a fair procedure that this should be conducted in accordance with a clear process that has been communicated to stakeholders, so that they understand the criteria that will be applied in decision-making and are able to take part fully and effectively. Conversely, it is well recognised that an approach whereby a process communicated to stakeholders is either disregarded or is developed or changed during the course of a procedure will almost certainly prejudice the ability of stakeholders to participate effectively and is likely to be unfair. An opaque and changing process results in prejudice to participants: a) because there is no certainty as to the criteria and approach that will guide decisions, and b) because it is patently impossible for stakeholders to participate in a process that has not been properly defined or communicated and where the information required for the purposes of decision making has not been adequately described.

The requirement for a clear, well defined and adequately communicated process is established:

- As a matter of fairness under English Administrative Law; and
- In the context of measures which control directly or indirectly the prices of medicinal products and whether they are covered by national insurance systems, in accordance with the EU Transparency Directive 105/89/EEC, which requires that such measures should be based on published criteria.

Therefore, if NICE's procedures are to be conducted fairly, it is necessary that these should be carried out in accordance with NICE's published process guides, which expressly intend that consultees and commentators should be involved and participate in the various procedures; this is possible only if the process is known and communicated, and is inconsistent with a procedure that is poorly described and changes during the course of the evaluation.

The evaluation of sebelipase alfa has failed to meet these standards of fairness.

Procedural unfairness in the evaluation of sebelipase alfa

The procedure applicable to the evaluation of sebelipase alfa was the Interim Process Guide for Highly Specialised Technology Evaluations, dated May 2013 (the Interim Process Guide). The Interim Process Guide is described as "an outline process" (paragraph 3) and states that in certain respects, the procedure will be similar to the existing technology appraisal process (e.g. in relation to selection of specialists and experts (paragraph 7) and consultation (paragraph 13)). There was no other procedure or guidance issued by NICE in relation to the HST procedure when the evaluation of sebelipase alfa was commenced in 2015 or when Alexion was required to make a submission for the purposes of the evaluation in October 2015.

However the evaluation of sebelipase alfa diverted from the Interim Process Guide and the procedure

evolved to include important requirements that are not mentioned in the Interim Process Guide, the substance of which were inadequately explained and remain unclear to Alexion, other stakeholders and, it seems, to the Evaluation Committee. Examples of these developments are set out below:

(a) The requirement for submission of a Managed Access Agreement, even though this is not mentioned in the Interim Process Guide and in circumstances where there is no published guidance as to the form or content or who should be involved in preparation, the timing for achieving this and when it should be carried out.

The Interim Process Guide includes no reference to any requirement for a Managed Access Agreement (MAA) in the context of an HST evaluation.

Alexion was first notified of the possibility of an MAA as an option that we might wish to consider, during discussions with at NICE in August 2015 regarding the decision problem for the HST evaluation of sebelipase alfa. We were, at that stage, provided with no guidance regarding the definition of an MAA, the scope or the elements that the Evaluation Committee might wish to see included within such an agreement, save for an outline template document, sent to us on 3 September 2015, which was essentially limited to headings and included no information regarding the detail of the matters to be included.

While no explicit direction was given to Alexion and other stakeholders, based on advice received from NICE in relation to asfotase alfa, we started to consider an MAA for sebelipase alfa following the first meeting of the Evaluation Committee in January 2016. Preliminary discussions between stakeholders commenced in February 2016; however, development of an MAA was prejudiced by the fact that NICE's procedures do not address the requirement for and preparation of an MAA and NICE had issued no specific direction and did not facilitate the participation of clinical experts, patient organisations and NHS England in the development of an MAA. As such, stakeholders had initially declined Alexion's invitation to engage on an MAA. Ultimately, discussions between stakeholder groups were arranged following intervention by NHS England . While, therefore a draft MAA was submitted to NICE in response to consultation on the first ECD, at this stage there had been only limited involvement by stakeholders.

The draft MAA for sebelipase alfa was considered by the Evaluation Committee during its second meeting on 22 March 2016 (the draft MAA for another HST, asfotase alfa, was also discussed), however there was still little guidance from the Committee as to the form and required content for an MAA, either in general or in the specific context of either product. Following further requests by Alexion for clarification from NICE as to Evaluation Committee requirements for an MAA, on 7 April 2016, we received a letter from NICE which purported to provide guidance in relation to asfotase alfa, although little substantive detail was included. The letter advised that, in developing an MAA for asfotase alfa, we should use "the MAA format and headings that have been used for the previous evaluation" [the only MAA approved by the Evaluation Committee at that stage was that relating to elosulfase alfa], even though substantial parts of that MAA were commercial in confidence and could not therefore act as a guide. The letter of 7 April, also stated that, rather than being facilitated by NICE, Alexion should "work

with clinical experts and relevant patient groups to capture the feedback contained in this letter...." This letter was followed by a telephone call with when she stated that Alexion should consider the letter of 7 April 2016 applicable to sebelipase alfa, even though this HST was not considered or referenced in the letter.

Work on the MAA therefore principally took place following the email of 7 April 2016 and after the second meeting of the Evaluation Committee on 22 March 2016 and issue of the second ECD on 26 April 2016. In preparing a revised MAA, Alexion worked with a group of relevant clinical experts (including Consultant in Paediatric Inherited Metabolic Diseases, The Willink Centre, St Marys Hospital, Manchester, Consultant in General Medicine and Metabolic Diseases, Addenbrookes Hospital, Cambridge, Consultant in Inherited Metabolic Disease, National Hospital for Neurology and Neurosurgery, London, Professor of Paediatric Hepatology, Kings College Hospital, London, Consultant in Inherited Metabolic Diseases, Birmingham Children's Hospital and Consultant in Adult Metabolic Medicine, Honorary Senior Lecturer, Salford Royal Foundation NHS Trust, Manchester), a patient group representative and NHS England. A revised MAA agreed by the listed contributors was submitted to NICE on 25 May 2016 and was considered by the Evaluation Committee at the third meeting on 20 July 2016.

Despite the agreement between stakeholders, including the listed group of clinical and patient experts, the Committee continues to criticise the proposed MAA, stating at paragraph 5.10 of the FED:

> "....it still had some concerns that it had not been provided with sufficient justification as to how the criteria would ensure that, in light of the heterogeneous patient population with LAL deficiency and the weak evidence base, the population would be restricted to only people who would gain most benefit from sebelipase alfa treatment and that none of those who would gain most benefit would be excluded from treatment".

However, while FED states at paragraph 5.9 that "the Committee discussed the content of the managed access agreement given its advice to the company on what it would expect of a complete managed access agreement for sebelipase alfa", no specific guidance has been issued by NICE or the Committee in relation to how such matters should be approached in an MAA in the context of an ultra-orphan disease or at all.

The lack of clear direction from NICE has resulted in confusion as to the roles of the various stakeholders in developing the MAA and has prejudiced discussion regarding arrangements. The current situation, where we face objections from the Evaluation Committee, as noted in the FED, to the form and content of an MAA agreed by key stakeholders in this evaluation, demonstrates that, in the absence of a clear procedure and guidance, there is no common understanding between stakeholders and the Committee as to what should be included in a MAA, how this should be structured, or the basis upon which the MAA will be evaluated by the Committee.

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(b) The Committee's belated requirement for a protocol and analysis plan to support the Managed Access Agreement, even though these are not mentioned in the Interim Process Guide and were not required in the evaluation of elosulfase alfa, to which Alexion was referred by NICE as a precedent

In circumstances where the Interim Process Guide does not include any reference to a MAA, it does not refer to any requirement for a protocol or analysis plan to accompany such MAA. In fact the only substantive guidance provided to Alexion in relation to the MAA, was that we should follow the precedent set by elosulfase alfa ; no protocol or statistical analysis plan was submitted or required by the Committee in that evaluation.

Nevertheless, the FED raises for the first time at paragraph 5.11, a criticism by the Committee:

> "...it would have preferred the company to submit a detailed data collection protocol and analysis plan to more fully explore the long-term effects of sebelipase alfa treatment".

This criticism is advanced, even though NICE's procedures make no reference to these documents and neither the Committee nor NICE nor any other person had suggested in any document in this evaluation prior to the FED, that a data collection protocol or analysis plane was needed. The only reference to a data collection protocol or analysis plan, prior to the FED, was a passing reference by the Committee Chair, during discussions at the July meeting. No guidance has been provided at any time as to the requirement for such documents or their structure or content.

The current criticisms in the FED regarding the absence of protocol and analysis plan to support the MAA, therefore create a conflict between advice provided to Alexion by NICE (which directed us to follow the precedent set in the elosulfase alfa evaluation, where there was no protocol or analysis plan), and the current requirements of the Committee, in circumstances where the published process provides no assistance.

(c) The procedure for agreeing commercial terms with NHS England

The Interim Process Guide includes no procedure for agreeing commercial terms between manufacturers and NHS England and no written guidance is available. As a consequence, in December 2015, Alexion submitted an application for a patient access scheme (PAS) to the Department of Health and then to PASLU, in accordance with NICE's standard procedures and encouraged by NICE. Ultimately after a protracted consideration by PASLU, which resulted in delay to the HST evaluation, the PAS was considered by the PASLU Expert Panel on 21 July 2016. Following this meeting we were invited to submit some additional information in relation to our PAS; this was provided in early August 2016; we have however heard nothing further from PASLU or the Department of Health and have still not been notified of any definitive outcome, some 15 months after proposing the PAS.

We believe (although we have received no formal notification) that while Alexion was

encouraged by NICE to utilise the PAS process, their view has now altered and NICE seems now to believe that commercial terms for HST products should be negotiated directly between the manufacturer and NHS England. We were informed of this potential route for the first time during the telephone call with and n December 2015 in relation to the HST evaluation of asfotase alfa, but advised to consider pursuing it in parallel with our application for a PAS.

Following discussions with stakeholders to develop an MAA, Alexion contacted NHS England by email on 26 May 2016, in order to commence negotiation of commercial terms for the supply of sebelipase alfa. While we met with and of NHS England on 22 June 2016, they indicated that, in the absence of a positive direction from NICE and in circumstances where the Evaluation Committee had not recommended use of sebelipase alfa in any patients even on a provisional basis in the second ECD, NHS England was not able to discuss commercial terms.

Therefore, in the absence of any response to the PAS offered by Alexion and any guidance to either Alexion or NHS England there was no possibility for any formal negotiation of commercial terms prior to the final meeting of the Evaluation Committee in November 2016. Alexion submitted a substantial commercial proposal to NICE for consideration by the Committee at that meeting, but this proposal received no input or approval from NHS England.

Alexion made clear to the Committee, in its submission dated 18 October 2016, repeated in an email dated 10 November 2016 and further reiterated at the meeting itself, its willingness to continue to negotiate with NHS England in the context of appropriate direction from NICE (and the requirement for such direction was also confirmed by of NHS England). However those submissions have apparently been disregarded by the Committee even though the FED makes clear that the principal barrier to a positive recommendation, which would allow patients to access life-saving treatment, is cost. By way of example, the FED states at paragraph 5.27:

> "However [the Committee] considered that the costs of sebelipase alfa still remained too high given the nature and size of the overall benefits and the important clinical uncertainties."

This is an impossible and wholly unacceptable situation. Alexion has repeatedly indicated its willingness to discuss commercial terms with NHS England but is prevented from doing so as a result of the lack of proper direction in NICE's procedures.

(d) Consistency and fairness in the procedure followed in different Highly Specialised Technology evaluations and the role of NICE

The lack of an adequately defined, published process for HST evaluations has resulted in uncertainty on the part of both consultees and NICE's staff as to the requirements of the procedure during the evaluation of sebelipase alfa and inconsistency with the approach followed in other evaluations.

- As described above, the arrangements for proposal of commercial terms by the manufacturer are uncertain and Alexion has received changing information during the course of the current evaluation, initially being advised to submit an application for a PAS through PASLU in the usual way and subsequently being notified that commercial terms should be negotiated with NHS England.

- In early November 2016, Alexion was encouraged by NICE staff to attend the November meeting, where a non-public discussion was arranged, to explain its willingness to engage with NHS England with regard to further commercial terms for the MAA-defined population. Despite Alexion's repeated declarations of its willingness to discuss additional commercial terms and the indications provided by NICE's staff, the Committee nonetheless published an FED, rather than allowing for further discussion.

- The involvement of NICE's staff in facilitating development of a MAA is not described in any written procedure and a substantially different approach was followed during the evaluation of sebelipase alfa to that taken in the context of the evaluation of elosulfase alfa. Biomarin has informed Alexion that NICE's staff provided them with detailed guidance on the content of an MAA, organised discussions between stakeholders to agree an MAA for elosulfase alfa and generally assisted the process to support stakeholders proceeding through the evaluation. However, even though there is no adequate published procedure and despite repeated requests by Alexion, NICE declined to provide any adequate information regarding the purpose or content of the MAA required for sebelipase alfa and refused to facilitate discussions between stakeholders to develop an MAA or between NHS England and Alexion to agree commercial terms. The lack of clear direction from NICE was highly prejudicial to the evaluation of sebelipase alfa and contrasted with the collaborative approach followed with elosulfase alfa.

Conclusion

In summary, the absence of a clear process and specifically, proper direction in relation to the formulation and submission of a MAA and the arrangements for negotiating commercial terms has, in our submission, resulted in the negative guidance in the current FED in relation to use of sebelipase alfa in people with LAL deficiency. In other words, the lack of a proper procedure has resulted in a MAA which is subject to criticism by the Evaluation Committee, despite being agreed by all stakeholders, and has also created a situation where it continues to be frankly impossible, as a result of uncertainty in the respective roles of the Evaluation Committee, NICE and stakeholders, for Alexion to negotiate commercial terms for the supply of sebelipase alfa to the MAA population, with NHS England.

1.2. There has been no effective consultation on the proposed recommendations for sebelipase alfa in the context of the managed access agreement.

Where a public body has committed to consultation, fairness requires that where there is a material change in the evidence base or considerations for NICE's recommendations, there should be effective consultation on the Committee's proposals. Paragraph 3.7.31 of NICE's Guide to the Processes of

Technology Appraisal (incorporated by the Interim Process Guide) states:

> "When consultees and commentators submit comments and/or new evidence that lead to a substantial revision of the ACD, involving a major change in the recommendations, considerations and/or evidence base, the centre director or programme director and the chair of the appraisal committee will decide whether it is necessary to prepare another ACD. If so, the consultation process will be repeated".

However the consultation which preceded the FED was inadequate.

In view of the absence of any adequate procedural guidance relating to the introduction and preparation of a MAA into the HST evaluation process, Alexion was able only to submit a draft MAA at the time of the second Evaluation Committee meeting which ultimately resulted in issue of the second ECD for sebelipase alfa. The second ECD recognises that the draft MAA was incomplete, it refers to the document as "the company's managed access proposal" (paragraphs 1.1 and 5.21); comments that "no associated estimates of costs and benefits were supplied by the company" (paragraph 1.1); and states that the proposal "had not been finalised with NHS England" (paragraph 5.21).

Following issue of the second ECD, substantial further work was undertaken by stakeholders, namely clinical experts, patient organisations, NHS England and Alexion, resulting in a substantially revised MAA, submitted to NICE on 25 May 2016. This revised MAA included detailed proposals, agreed between stakeholders, for starting and stopping treatment with sebelipase alfa and arrangements for data collection.

The Committee's response to these extensive new proposals was issued in the FED, but has not previously been considered or subject to consultation. In circumstances where appeal does not provide an adequate substitute for consultation - the grounds for appeal are limited and commentators and the public may not participate - the failure to carry out effective consultation on the current proposals, has excluded potentially important commentary on the FED and represents a procedural deficiency in the current recommendations.

1.3. The Committee's assessment of value for money is unfair and fails to consider the population of patients eligible for treatment within the managed access agreement

The MAA prepared by clinical experts, patient organisations, NHS England and Alexion and submitted in May 2016, substantially reduced the patients with LAL deficiency who would receive treatment with sebelipase alfa, from those eligible in accordance with the marketing authorisation, to a subgroup of patients who have the highest clinical need and would therefore be expected to benefit most from therapy. The Evaluation Committee has failed to take this into account in any way in the context of its assessment of the value for money associated with use of the product.

By way of example, at paragraph 5.17 of the first ECD, issued in February 2016, the Committee stated

> "Following the Committee meeting, the Committee asked the ERG to run the model with [its preferred] assumptions applied. The Committee noted that applying these

assumptions resulted in a total QALY gain of 17.15 with sebelipase alfa and 10.52 with best supportive care, (incremental QALYs of 6.64,.....)".

Following issue of the first ECD a draft MAA was prepared and this was refined during consultation on the second ECD in discussion with a group of clinical experts, patient organisations and NHS England. The MAA restricted treatment to patients with LAL deficiency at the highest clinical need and those who would be expected to benefit most from treatment. However despite the restriction under the proposed MAA, the Committee's conclusions regarding the total QALY gains associated with sebelipase alfa treatment, as reported at paragraph 5.21 of the FED, were unchanged:

> "Therefore, in the committee's preferred analysis, sebelipase alfa was associated with a total quality-adjusted life year (QALY) gain of 17.15, compared with 10.52 QALYs for best supportive care (incremental QALY gain of 6.64 probabilistic result)."

The Evaluation Committee's unchanged conclusion, following Alexion's response to the first ECD, which accompanied the revised MAA proposed in May 2016, suggests that the revised MAA was not even considered by the Evaluation Committee in reaching its conclusions on value for money. As Alexion stated in its response to Section 5.18 of the first ECD:

> "The CCA [cost-consequence analysis] developed for NICE was parameterised based on the sebelipase alfa clinical trials LAL-CL02 (ARISE) and LAL-CL03 [...] The base case results reflect the impact of sebelipase alfa treatment vs. best supportive care (BSC) in the broader LAL Deficiency population. As a result, the extent to which the CCA base case results reflect the value proposition of sebelipase alfa in the population covered by the Marketing Authorisation depends on the similarity of the MAA clinical criteria for treatment and the clinical profile of patients included in the LAL-CL02 and LAL-CL03 trials. [...] considering that the provisions of the proposed MAA will determine patient access to treatment, the relevant patient population in which value for money should be assessed is that meeting the eligibility criteria of the proposed MAA, rather than the broader population that was addressed in Alexion's previous submissions, and reflected in the CCA base case results.

While treatment efficacy in a patient population matching the MAA population could not be measured from the clinical trials for sebelipase alfa, this would not preclude consideration of the impact of the MAA on value for money, even if the precise effect on QALYs gained could not be calculated. However there is no reference to the MAA when considering the value for money of sebelipase alfa in the FED, underscored by the fact that the Evaluation Committee's preferred analysis did not change from the ERG's analysis (i.e., yielding 6.64 incremental QALYs) submitted before the MAA proposed in May 2016 was even developed.

1.4. The Committee has provided no adequate reasons for its conclusions regarding the determination of the population of patients eligible for treatment within the proposed managed access agreement for sebelipase alfa

The eligibility criteria for sebelipase alfa treatment under the apposed MAA are set out at paragraph 4.37 of the FED. In summary:

- Eligibility for treatment under the MAA is limited to:
    - all babies presenting with LAL deficiency aged under 1 year;
    - people who present with LAL deficiency aged 1-18 years with malabsorption, hepatomegaly with persistently elevated transaminases, signs of liver fibrosis (defined by an Ishak score of at least 1) or signs of liver dysfunction; and
    - people who present with LAL deficiency aged over 18 years with liver fibrosis (defined by an Ishak score of at least 2).
- Treatment would be discontinued where the disease does not respond to therapy, defined as:
    - persistent failure to thrive or progression to liver failure (babies under 1 year);
    - not crossing an upwards centile line (children with malabsorption);
    - an increase in spleen volume of greater than 10% or progressive liver disease (children over 1 year and adults);

  or failure to attend clinics or in patients who have undergone liver transplant.

However, at paragraph 5.10 of the FED, the Evaluation Committee refers to the revised MAA for sebelipase alfa and states:

> " The committee considered that the statement in the managed access agreement that all babies under 1 year presenting with LAL deficiency and people over 18 years with LAL deficiency and liver fibrosis (with an Ishak score equal to or higher than 3) would start treatment with sebelipase alfa reflected the clinical experts' preferences. It noted that the criteria for starting treatment in people presenting between 1 and 18 years were based on whether the person had malabsorption, hepatomegaly, liver fibrosis or liver dysfunction. The committee noted that the revised managed access proposal did not allow people to restart treatment with sebelipase alfa. It concluded that the population for whom sebelipase alfa would be considered within the revised managed access agreement was identified more objectively that in the initial proposals. The committee acknowledged that the starting and stopping criteria would restrict the number of eligible patients and therefore limit the overall budget impact. However, it still had some concerns that it had not been provided with sufficient justification as to how the criteria would ensure that, in light of the heterogeneous patient population with LAL deficiency and the weak evidence base, the population would be restricted to only people who would gain most benefit from sebelipase alfa treatment, and that none of those who would gain most benefit would be excluded from treatment".

The criteria listed at paragraph 4.37 have been prepared by clinicians with expertise in the management of patients with LAL deficiency, on the basis that they are objective and identify those patients, from the "heterogeneous" population, who have greatest clinical need and would therefore derive most benefit from enzyme replacement treatment with sebelipase alfa. The high clinical need of the MAA population and the benefits obtained appears to be accepted by the Evaluation Committee as shown, for example by their conclusions at paragraph 5.4. In these circumstances, the Committee is required to provide adequate reasons to support its criticisms of the proposed MAA at paragraph 5.10 and why it disagrees with the conclusions of the clinical experts in relation to identification of patients who are most likely to benefit from treatment, including, it seems, babies where treatment is needed to prevent death before age one year. In the absence of such reasons, including any areas where the Committee disagrees with the clinical experts and why, there can be no effective consultation and no proper response to the Committee's concerns.

Similarly, the Committee refers to "the weak evidence base" for sebelipase alfa as a reason for questioning the proposed MAA. However, the Evaluation Committee has recognised the views of the clinical experts that sebelipase alfa is considered to be "a step change in managing [LAL deficiency]" (paragraph 5.4) and has expressed no disagreement with this view. Inevitably, in the context of an ultra-orphan disease, the data will be more limited that those available for common medical conditions: this is true of all rare diseases and is one of the reasons why data collection for sebelipase alfa, post-authorisation, is mandated by regulatory authorities and potentially implemented in the context of a MAA. If the Committee intends to suggest that the data which prompted regulatory approval on an accelerated basis by the European Commission, taken together with a proposed MAA to manage uncertainty, are still insufficient for NICE's purposes, it should say so and should specify how long a period of follow-up would be required before it will be satisfied that the data (already viewed as a step change by clinical experts) reduce uncertainty to acceptable levels for the purposes of patients in England.

1.5. The Committee has failed adequately to take into account the benefits of sebelipase alfa in infants with rapidly progressing lysosomal acid lipase deficiency

The Evaluation Committee's focus on base case results in the FED failed to take into account all of the benefits of treatment, specifically in infants presenting with LAL deficiency.

Section 5.22 of the FED states:

"[The Evaluation Committee] discussed the overall value of sebelipase alfa, taking into account both its health benefits (the range of estimates presented by the company and ERG was between 0 and 21.4 additional QALYs, and the committee's preferred estimate was up to 6.64 additional QALYs) and associated costs, in the context of other highly specialised technologies."

This statement fails to account for the fact that Alexion's estimate of 21.4 additional QALYs associated with sebelipase alfa treatment, was the average across the patient population identified as eligible for treatment under the MAA; this average consisted of a weighting of incremental QALYs of 27.4 for infants presenting with the disease and 18.5 for children and adults presenting with the disease, as reflected in Alexion's response to consultation on the second ECD submitted together with the consensus MAA

proposed by stakeholders, in May 2016 (see the response to Section 5.18 of the first ECD). Alexion's response to the second ECD also explained that incremental costs consisted of for infants and for children and adults.

By focussing on the health benefits across the MAA population, the conclusions of the Evaluation Committee did not therefore take into account the magnitude of benefits experienced by infants, owing to the significant survival benefits treatment confers on such patients and the compelling data from the LAL-CL03 study which showed a 5 out 0f 9 infants in this treatment cohort had survived at 3 years when treatment with sebelipase alfa was commenced within the first year. These infants also had achieved their development milestones, These matters are not addressed at all in the Committee's conclusions.

In addition, the range of benefits, and associated costs, considered fails to account for the fact that treatment in infants presenting with the disease yielded approximately 1.5 times (i.e., 27.4 / 18.5) the benefit as in children and adults, at only approximately 1.1 times the cost. Patients with presentation in infancy are typically managed with dosing of 3 to 5 mg/kg (NB this is an off-label dose) of body weight every week, whereas patients with later presentation are managed with dosing of 1 mg/kg every other week. As such, patients with presentation in infancy require 6 to 10 times the drug for a certain body weight, but due to the annual per-patient cost cap, have only marginally higher (i.e., 1.1 times) costs, reflecting a meaningful difference in value for money across these patient populations. However these facts do not appear to have been considered by the Evaluation Committee when formulating its conclusions regarding use of sebelipase alfa in infants.

1.6. The exclusion of a clinical expert from the meeting of the Evaluation Committee in November 2016 was unfair and is likely to have prejudiced this evaluation

One of the clinical experts for the evaluation of sebelipase alfa, Dr Simon Jones, was unable to attend the meeting of the Evaluation Committee in November 2016, as he could not rearrange his clinical commitments. Dr Jones was aware of the potential importance of his contribution at the meeting and therefore asked NICE if he could dial-in to the meeting by telephone. While this arrangement was agreed, unfortunately, there was a technical problem, which resulted in Dr Jones being disconnected. Following this technical issue, there was no attempt made by NICE to communicate with him regarding the difficulty or to allow him to participate through another route (e.g. by using his mobile phone).

The November meeting of the Evaluation Committee included important discussions regarding the revised proposals submitted by Alexion, as well as crucial new clinical data (e.g. 1 year liver biopsy results demonstrating end organ effects of sebelipase alfa treatment as opposed to surrogate markers previously criticised by the Committee). These data are so remarkable that, despite there being no basis for this suspicion, one member of the Evaluation Committee questioned whether Alexion had manipulated the results. While the question was patently incorrect and unjustified, it demonstrates that the opinions of experts are likely to have been highly influential in assisting the Committee to understand and interpret the data and the failure by NICE to facilitate the participation of a key clinical expert in this discussion represents a flaw in the procedure, which is likely to have prejudiced the recommendations in the FED.

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1.7. The Committee has provided no reasons to justify its criticisms of the trial data for use of sebelipase alfa in babies presenting before 6 months

At paragraph 5.5 of the FED, the Committee refers to the evidence for the efficacy of sebelipase alfa in babies presenting before 6 months with rapidly progressive LAL deficiency and to the criticism by the Evidence Review Group (ERG) that the use of historical controls may have biased the results in favour of sebelipase alfa, because babies receiving best supportive care in the past may potentially have had poorer outcomes than similar babies treated today. The basis for this view is seemingly that standards of best supportive care generally have improved. While the Committee notes the views of clinical experts "that any changes in best supportive care had not improved survival in this patient population", the Committee proceeds to express doubt about the benefits of sebelipase alfa treatment in babies, in part because "no robust comparative data were available". No explanation is given for the Committee's concerns other than the earlier reference to the ERG's criticisms of historical controls and the Committee provides no reasons for disregarding the opinions of the clinical experts.

In circumstances where a clinical trial comparing sebelipase alfa with best supportive care would now be unethical, and where the clinical experts have explained that in the context of a metabolic disease, improvements in best supportive care will not improve survival, the committee's residual concerns over trial design, require to be explained and justified. In the absence of such explanations, it is impossible for Alexion to respond to the conclusions expressed in the FED.

1.8. The Committee has failed to consider the status of children with juvenile-onset LAL-D in accordance with the provisions of the Human Rights Act 1998

The Appeal Panel who considered the appeal against the Final Appraisal Determination for dinutuximab for treating high-risk neuroblastoma considered whether the failure to recommend that technology as a treatment option was contrary to human rights legislation, in view of the particular status of patients eligible for treatment in accordance with its marketing authorisation, as children. The Panel agreed that articles 2, 8 and 14 of the European Convention on Human Rights were engaged by the decision and expressed the view that the status of patients as children was also a factor to be taken into account in accordance with English public law principles. While recognising that NICE was not obliged to give the status of children "paramount weight", the Panel found that the Appraisal Committee was required to consider such status as a relevant issue and, in circumstances where the appraisal documents did not record such consideration, was not satisfied that the Committee's treatment of the issue met that requirement.

Similar considerations are applicable to the current HST evaluation of sebelipase alfa and, in particular, to the Evaluation Committee's assessment of use of the technology in babies with LAL deficiency, where the FED does not recommend treatment, despite recognising that sebelipase alfa may be life-saving and that there is a compelling clinical need, and in children.

Alexion submits that the Committee is required to take into account the particular status of children who may receive treatment with sebelipase alfa in the course of its evaluation. As stated by the Appeal Panel in the dinutuximab appeal:

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> "Provided the Committee asks itself whether its approach should change to reflect the fact that the population targeted for this technology are children, and gives a reasoned answer, it will have corrected the error identified by the Panel. What it should then do will be a matter for its judgement and will depend on whether or not it considers a different approach is needed and the evidence available to it"

Such consideration is not documented in the evaluation documents for sebelipase alfa (including in the context of equalities considerations and social value judgements) and must therefore be assumed to have been absent from the Committee's review of the technology to date.

1.9. In reaching its conclusions regarding sebelipase alfa, the Committee has failed to take into account relevant evidence

(a) While the Committee recognised at paragraph 5.18 of the FED that the ERG's conclusions on preferred utility values were likely to be too conservative, it still preferred them to the values proposed by Alexion, but failed to take any account of the effect of this conservative approach in its ultimate conclusions.

At paragraph 5.18 of the FED, the Committee states:

> "The Committee concluded that there were issues with estimates of utility values identified by both the company and ERG because they had not been derived from people with LAL deficiency. It also considered that the company's utility values might be overestimates of the true utility values, and the ERG's values might be underestimates. It concluded that the true utility values were likely to be closer to the ERG's estimates because it was unlikely that people with LAL deficiency experienced a better quality of life than age-matched people without a chronic condition".

However, no recognition of this conservative approach is provided by the assessment at paragraph 5.21, which simply incorporates the ERG's preferred utility values without any admission that the correct value is likely to be more favourable.

(b) In addition, while the clinical trial data for sebelipase alfa focussed on effects of LAL deficiency on the liver, this means that other potential benefits of sebelipase alfa treatment (including effects on the cardiovascular system) have been disregarded. Alexion submits that in reaching its overall conclusions regarding sebelipase alfa therapy the Committee should have recognised that certain benefits of treatment had not been taken into account in the economic analysis.

2. GROUND 2: THE RECOMMENDATION IS UNREASONABLE IN THE LIGHT OF THE EVIDENCE SUBMITTED TO NICE

2.1. The Committee's criticism of Alexion for failing to incorporate collection of non-invasive measures of liver damage in the proposed managed access agreement are unreasonable in circumstances where such measures have not been validated in LAL deficiency.

At paragraph 5.11 of the FED, the Committee considers the arrangements for data collection in the proposed MAA and comments.

> "The Committee noted that in children under 18 years there were no direct measures of liver damage in the outcomes listed. The Committee stated that non-invasive measures of liver damage (which do not involve a biopsy) are available and that measuring definite clinical outcomes rather than surrogate markers was preferable".

While the Committee does not identify the "the non-invasive measures of liver damage" to which it refers, the only non-invasive measure of which we are aware is Fibroscan, a methodology which uses elastography, a technique similar to ultrasound. However, while we are aware that such a method may be used for the assessment of other causes of liver disease, it has not been validated in LAL deficiency, as was discussed with the Committee after the second ECD, and accordingly the results of assessment would be unreliable and difficult to interpret.

The MAA includes Fibroscan as a non-invasive measure at baseline and at assessment visits for children and adults. As it has not been validated in LAL deficiency, any data collected would be exploratory, in an attempt to validate this measure. Other, well-validated measures of liver disease have been included in the MAA on the advice of hepatology experts, including other imaging techniques. In these circumstances we believe the Committee's criticism of Alexion for failing to reference non-invasive measures of liver damage in the proposed MAA, and their conclusion that the clinical outcome measures chosen were not the most relevant for capturing clinical effectiveness of sebelipase alfa, are unreasonable

2.2. The Committee's explanation for preferring the utility values selected by the Evidence Review Group does not justify the values selected

However, as described at paragraph 4.28 of the FED, the Evidence Review Group (ERG) carried out various sensitivity analyses to explore the effect of changing the utility values used in the economic model from those submitted by Alexion. In particular:

- The ERG suggested use of utility values from Crossan et al (2015)[7], which considered assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease, rather than the values from Mahady et al (2012)[8] as proposed by Alexion, on the basis that "the ERG

[7] Crossan C, et al. Cost-effectiveness of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease: systematic review and economic evaluation. Health Technol Assess. 2015;19(9):1-409

[8] Mahady SE,et al. Pioglitazone and vitamin E for nonalcoholic steatohepatitis: a cost utility analysis. Hepatology. 2012;56(6):2172-2179

considered that the way the company had identified utility values used in its model had not been transparently described".

- In addition, the ERG criticised the utility values proposed by Alexion because these were "higher than those estimated for the general UK population". In order to address this second point, the ERG carried out a sensitivity analysis which capped the utility values used in the model, so that these did not exceed those of the general population.

In reaching its conclusions regarding utility values, the Committee states at paragraph 5.18 of the FED that it considered that the true utility values were likely to be closer to the ERG's estimates and gave its reasons as "it was unlikely that people with LAL deficiency experienced a better quality of life than age-matched people without a chronic condition".

The Committee has therefore accepted both of the ERG's adjustments, rather than simply the analysis described under the second bullet above, under the misapprehension that use of the Crossan data corrects for use of utility values which exceed those of the general UK population. This is incorrect and unreasonable.

We submit that the Committee should have used the ERG's adjustment described under the second bullet above (accepted by Alexion in its response to the ECD), but continued to rely on the Mahady et al data proposed by Alexion rather than data proposed by Crossan et al. As previously stated by Alexion, the Crossan data, which limit the highest utility value associated with LAL deficiency tc which is the health utility associated with a 100 year old in the UK population, appears highly implausible in circumstances where LAL deficiency without compensated cirrhosis, decompensated cirrhosis or hepatocellular carcinoma is associated with minimal symptoms. This deficiency in the Crossan data has not seemingly been recognised by the Committee.

THE DETERMINATION OF THIS APPEAL

Alexion requests an oral hearing for the determination of this appeal.

REMEDY FOLLOWING APPEAL

Alexion respectfully requests the Appeal Panel to direct

- That the procedure for preparing a MAA and the content and purpose of such an agreement should be clearly stated in writing and issued to consultees;

- That the procedure for the offer and negotiation of commercial terms in the context of an HST evaluation, should be clearly explained in writing and issued to consultees;

- That the recommendations in current FED should be subject to effective consultation and that that the results should be taken into account by the Evaluation Committee before guidance is finalised

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- That the Evaluation Committee should give additional consideration to the evaluation of sebelipase alfa at a further meeting and should issue a further ECD or FED:
    - That the further meeting of the Evaluation Committee should be scheduled with adequate notice giving consultees and clinical specialists opportunity to attend;
    - That the Committee should take into account the proposed MAA and all relevant evidence when reaching its conclusions
    - That the further ECD or FED issued by the Evaluation Committee should provide adequate reasons to explain the conclusions reached by the Committee including (if relevant):
        - in relation to any objections to starting and stopping criteria as described in the MAA;
        - In relation to criticisms of the clinical trial programme for sebelipase alfa;
    - That the Committee's proposals for data collection in the MAA should be limited to measures validated in LAL deficiency;
    - The Committee should reconsider the compelling evidence for benefits in infants with LAL deficiency treated with sebelipase alfa
    - The recommendations should take account of all potential benefits of sebelipase alfa treatment
    - That the Committee should take into account the status of children with juvenile-onset HPP in formulating its recommendations, in accordance with the Human Rights Act 1998.
    - That the Committee should reconsider its assessment of the benefits associated with sebelipase alfa treatment using utility values derived from Mahady et al (2012) rather than Crossan et al (2015).

[redacted]

Senior Vice President, Global Government Affairs