ALEXION

Mr Andy McKeon
Vice Chair
National Institute for Health and Clinical Excellence
10 Spring Gardens
London SW1A 2BU

23 March 2017

Dear Mr McKeon

Appeal against the Final Evaluation Determination for sebelipase alfa for the treatment of lysosomal acid lipase deficiency

Thank you for your letter dated 9 March 2017, setting out your preliminary view as to the admissibility of the points of appeal raised by Alexion in our Appeal Letter of 1 March 2017 and confirming that our appeal will be heard by NICE's Appeal Panel at an oral hearing.

We now provide further clarification in relation to the points of appeal identified in your letter, in advance of your final decision on admissibility. Our submissions are set out by reference to the individual points of appeal, using the same numbering as our Appeal Letter.

1. **Ground 1**

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**

Your view that this is a valid ground 1 appeal point is noted.

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

You express the preliminary view that this point of appeal should not be permitted to proceed. Your reasons for this view are:

- You say that NICE is under two obligations with respect to consultation: (a) it must ensure that consultees are sufficiently informed to make an intelligent response, must give them time to do so and consider their responses; and (b) where a draft recommendation changes substantially, it must consider whether to consult again.

- You suggest that the differences between the second ECD and FED in this evaluation are not such as to call for a third ECD. You say that our appeal point calls for a right of reply to the

Committee's treatment of our MAA, but express the view that this is not required either in accordance with NICE's processes or as a matter of fairness.

We do not agree with the analysis set out in your letter and strongly believe that a fair procedure requires that consultation should take place, based on the consensus proposals contained within the MAA. In particular, it is not only where a recommendation "changes substantially" that there is an obligation to carry out a further consultation, but where the basis for decision-making undergoes major change or where an important new option becomes available to the Committee, but is rejected.

A fair consultation must satisfy the principles established by the Supreme Court in R (Moseley) v Haringey LBC [2014] 1 WLR 394, which includes the obligation to consult on proposals which the public body has, itself, rejected.

Furthermore, the Government's "Consultation Principles" reissued in January 2016, refers to iterative consultation and the fact that consultation may be an ongoing process.

> "Consider whether informal iterative consultation is appropriate, using new digital tools and open, collaborative approaches. Consultation is not just about formal documents and responses. It is an on-going process".

Applying these principles to the evaluation of sebelipase alfa, the introduction of an MAA, agreed between key stakeholders (expert clinicians, patient representatives, NHS England and the manufacturer) fundamentally altered the way in which the product could be made available to patients with LAL Deficiency in England and created an option which had not been the subject of consultation by NICE. Consistent with the decision of the Supreme Court in Moseley, even though this option had been rejected by the Evaluation Committee, it should have been subject to iterative consultation, as envisaged by Consultation Principles, so that the responses could be taken into account before a final decision was reached on these important new proposals agreed by the major stakeholders in the process.

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.**

Your view that this is a valid ground 1 appeal point is noted.

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.**

Your view that this is a valid ground 1 appeal point is noted.

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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**

You express the preliminary view that this point of appeal should not be permitted to proceed. You suggest that the points set out in our appeal letter have been considered by the committee as set out at paragraph 5.23 of the FED.

At point 1.5 of our appeal we refer to the fact that the assessment of sebelipase alfa by the Evaluation Committee failed to address the particular benefits of treatment in infants with rapidly progressing LAL Deficiency as demonstrated by the fact that the Committee's consideration of overall value only deals with the entire eligible patient population. The Committee's conclusions in relation to the QALY benefits at paragraph 5.22 of the ECD refers only to the QALY's associated with the full patient population and disregards the increased benefits in infants. In particular, there is no reference to Alexion's assessment of the benefits specifically in infants (27.4 QALYs) or the assessment of benefits in this population by any other person. In addition, as explained in our appeal letter, the Committee failed to consider the costs in infants relative to the substantial benefits in this population.

Paragraph 5.23 of the FED addresses the value of treatment with sebelipase alfa in infants in only general terms. There is no indication that the Committee considered the QALY benefits of treatment in this population other than saying that "this group had greater incremental QALYs than the whole population, but the incremental costs were also higher". The Committee therefore failed to reach any specific conclusions or to carry out any analysis of whether the increased benefits exceeded any increased costs associated with treatment. In circumstances where there is no proper assessment of benefits, there is inadequate foundation for a conclusion, as stated by the Committee, that "it was not convinced that the benefits of treatment were sufficient to justify these very high costs".

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

You express the preliminary view that this point of appeal should not be permitted to proceed, unless Alexion can show that was the only person with clinical expertise available to the Committee that day and that the Committee were or at least arguably may have been unable to understand the clinical issues without his input. You refer to the decision of the Appeal Panel in TA360, which you say raised a similar issue.

We do not agree that the test is whether was the "only person with clinical expertise available to the Committee" at the November meeting. The evaluation of sebelipase alfa requires clinical expertise in several disciplines, not merely one. Whils' attended the November meeting of the Committee, he is an adult physician and has no experience of treating infantile disease. In contrast, s the world's leading expert on LAL Deficiency; he has treated more infants with

sebelipase alfa than any other physician worldwide and has experience both of infants dying following treatment and of survival. had been invited by NICE to attend the meeting of the Evaluation Committee in November 2016 and must therefore have been thought necessary to advise the Committee at that meeting. In the event, questions were asked about infant survival and outcomes by the Committee, which could not be adequately addressed in sence.

Furthermore, in circumstances where had indicated that he could not attend the meeting of the Evaluation Committee in person, NICE agreed that he should participate by telephone. However when technical difficulties made the initial attempt to join to the meeting challenging, NICE made no attempt to use alternative methods (e.g. a different telephone line) or even to inform him of what had transpired.

For completeness, the situation in this evaluation is not comparable in that of TA 360, where the issue considered by the Appeal Panel was whether additional clinical expertise should have been obtained in order to resolve disagreements between the experts present. In this case, it is not a question of disagreements between experts with relevant experience, but the fact that the Committee was without any relevant clinical expertise to advise on a central issue considered at the meeting.

In summary, Alexion believes that, having accepted that attendance at the meeting was desirable, NICE's failure to take reasonable steps to facilitate this was unfair and, for the reasons set out above, his non-attendance has prejudiced the outcome of this evaluation.

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

You express the preliminary view that this point of appeal should not be permitted to proceed on the basis that you interpret the FED (in particular paragraph 5.17) as indicating that the Committee did not accept the ERG's assessment of the benefits of sebelipase alfa compared with best supportive care and that you construe the reference to lack of robust comparative data as referring to the longer term benefits (e.g. whether the response to treatment is maintained and life expectancy fully restored).

We disagree that the statements in the FED are capable of the meaning you suggest. The fact that the Committee viewed the ERG's conclusions as conservative, does not mean that all of the ERG's criticisms were necessarily rejected by the Committee and, in particular, the Committee's doubts about the benefits of sebelipase alfa in babies in the absence of robust comparative" data can only mean that the Committee was critical of the lack of a direct head to head comparison as suggested by the ERG. In contrast, a reference to "comparative" data does not mean either long-term data or data relating to life-expectancy.

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Our interpretation of the Committee's statement, which is that the data in infants are criticised due to the absence of a control group in the studies is supported by the fact that the summary tabulation at the end of the FED references the Committee's concerns in this respect to paragraph 5.5 and 5.6 of the FED and not to paragraph 5.17.

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

Your view that this is a valid ground 1 appeal point is noted. We will provide any legal submissions 21 days in advance of the appeal hearing as requested.

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

Your view that this is a valid ground 1 appeal point is noted

2. **Ground 2**

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 D

Your view that this is a valid ground 2 appeal point is noted.

2.2. The Committee's explanation for preferring the ERG's utility values does not justify the values selected.

Your view that this is a valid ground 2 appeal point is noted

Alexion strongly believes that all of the appeal points raised in its Appeal Letter of 1 March 2017 are validly advanced. We have provided in this response, further clarification of the matters set out in your letter and would ask you please to confirm that all of our appeal points may proceed to a full hearing. If, however, you have further queries, we will be pleased to provide additional elaboration.

We look forward to receiving your response to this letter and your final decision in relation to the admissibility of our appeal.

Yours sincerely,

[redacted]

Senior Vice President, Global Government Affairs