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Worldwide Biopharmaceutical Businesses

Mr Tim Irish
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National Institute for Health & Care Excellence
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23 November 2020

Dear Mr Irish

Appeal against the Final Appraisal Determination for Tafamidis for Treating Transthyretin Amyloidosis with Cardiomyopathy

Thank you for your letter dated 9 November 2020, in which you provide your preliminary view of the admissibility of the points of appeal set out in Pfizer's appeal document submitted on 30 October 2020.

We now provide, as you suggest, additional submissions to elaborate or clarify those points of appeal where your preliminary view is that these should not proceed.

Ground 1(a) in making the assessment that preceded the recommendation, NICE has failed to act fairly

1.1 The Committee has failed to take into account relevant evidence or to explain why the diagnostic algorithm prepared by the National Amyloidosis Centre has not been accepted

You express the preliminary view that this point should not be referred to the Appeal Panel on the basis that: (a) the Committee was aware of the algorithm; (b) you say that they do not "reject" it; (c) they summarise the other evidence they received; and (d) conclude that there are still challenges in diagnosis.

In your letter you say that the FAD and appraisal documents have to be read together in order to understand the Committee's reasons for rejecting the diagnostic algorithm. We strongly disagree with this statement. While you do not define what is meant by "appraisal documents", these could include a substantial number of documents prepared by many stakeholders who are not, in contrast to the Committee, decision makers in this appraisal. The reasons for the conclusions of the Committee (the decision maker) are not provided by appraisal documents prepared by such stakeholders, unless these have been explicitly approved by the Committee and referenced in the FAD. It is plainly not for consultees to guess which submissions by which stakeholders are accepted by the Committee and form the basis for its conclusions and which have been rejected.

This point of appeal relates to the Committee's conclusion at paragraph 3.4 of the FAD "that there would still be challenges in diagnosing ATTR-CM". In response to the specific points you raise:

- In response to point (c), in reaching its conclusions, the Committee has referenced statements from two clinical experts that there were, in the past, challenges in diagnosing ATTR-CM (paragraph 3.3 of the FAD) but has failed to take account of (a) the written view of one those experts, Professor Hawkins from the National Amyloidosis Centre, that "*cardiac ATTR amyloidosis is now recognised to be a common and easily diagnosed disorder*" (b) the evidence of Professor Elliott given at the second Appraisal Committee meeting regarding the diagnosis of ATTR-CM; failure to take into account the key evidence from these two experts, which is not referenced at all in the FAD, represents a procedural deficiency in the conclusions reached by the Committee.

- In response to point (a), Pfizer does not suggest that the Committee was unaware of the algorithm; it is referenced at paragraph 3.4 of the FAD as quoted in our appeal letter.

- In response to point (b), the Committee concluded that, despite the availability of the algorithm, diagnosis of ATTR-CM would still present "challenges"; however in circumstances where the purpose of the algorithm (as recommended by EMA's CHMP) is the appropriate diagnosis of ATTR-CM and where the clinical experts advising this appraisal as well as international experts in the area, endorsed by multiple professional societies across Europe and the United States, have confirmed the validity of the algorithm, the conclusions of the Committee indicate that it does not accept that the algorithm forms a reliable basis for diagnosis (i.e. its intended purpose).

- In response to point (d), we agree that the Committee concluded that, despite the availability of scintigraphy (i.e. DPD scans) and the algorithm, there are still challenges in diagnosis, however our appeal is based on the fact that they failed to provide adequate reasons for that conclusion. In particular, the only two points conceivably raised by the Committee to justify its conclusion:

  (i) the fact that two clinical experts at the first Appraisal Committee meeting stated that amyloid deposits may be an incidental finding; and

  (ii) the reference in the European Public Assessment Report to difficulties in diagnosis of patients with NYHA class 1 without heart failure and to the need for procedures, such as biopsy and scintigraphy (i.e. DPD scans) for an accurate diagnosis.

  Neither of these points relied upon by the Committee took into account the provisions of the algorithm which addresses these issues and the evidence of Professor Elliott. In these circumstances, there is no explanation whatsoever in the FAD to explain the Committee's conclusion that "*even with DPD scans and a diagnostic pathway, there would still be challenges in diagnosing ATTR-CM*".

1.2 The Committee's conclusions regarding the diagnosis of ATTR-CM have misconstrued the European Public Assessment Report for tafamidis

You suggest that this point of appeal should proceed under Ground 2. Pfizer is content to proceed on that basis.

1.3 The Appraisal Committee's reference to the fact that the marketing authorisation for tafamidis does not specify starting and stopping rules based on the NYHA classification, relies on an irrelevant consideration

Your preliminary view is noted.

1.4 The Appraisal Committee's conclusion that it would not consider starting and stopping rules for tafamidis based on the NYHA classification system even though the NYHA system has been used in previous NICE appraisals is unexplained and potentially discriminatory

We are concerned that there has been some confusion in relation to this appeal point and strongly disagree with the preliminary view that it should not proceed to a hearing.

You say that there are three points here (a) that the decision is unexplained; (b) that it is inconsistent with past appraisals; and (c) that it is discriminatory. This misconstrues the issue raised by Pfizer which is, simply, the single point that no explanation has been provided to justify a different approach in this appraisal to that adopted in relation to other appraisals of other technologies which based treatment decisions on NYHA classification. Furthermore, that the requirement for reasons is enhanced where, as here, NYHA classification is accepted in some NICE guidance to measure severity of certain types of heart failure linked to certain characteristics and ethnicities, but not to other types of heart failure and the inconsistency is therefore potentially discriminatory.

You refer to NICE's broad expectation that appraisals will adopt a consistent approach, but say "*this must not be overstated where each appraisal is likely to turn on very different evidence bases*" and that you are not persuaded that "*the fact that past appraisal committees have felt able to make use of the NYHA when appraising different drugs for different conditions is of any relevance to the work of this committee….*" . In fact however, the issue is use of the NYHA classification to assess the severity of the same condition, heart failure, in multiple appraisals - but a conflicting and inconsistent approach being adopted in this case.

The NYHA classification is a generic tool used widely to assess symptoms of heart failure, irrespective of cause, in clinical practice. The Committee's conclusions in relation to the general reliability of the NYHA classification do not arise from the specific evidence base in this appraisal, but from a general objection, despite its widespread use, which is not shared by the appraisal committees in the appraisals listed in our appeal letter. There is, in particular, no suggestion either in the available scientific evidence or in the FAD that the NYHA classification is less reliable in assessing heart failure associated with ATTR-CM than heart failure due to any other cause.

However the fact that the Committee in this appraisal decided to reject use of NYHA classification as a basis for stopping rules, whereas NICE guidance following other appraisals has accepted use of NYHA, is a significant factor resulting in the Committee's negative decision. Consistency between appraisals is important for guidance to be credible and a substantial deviation from the approach followed in multiple other appraisals requires explanation. In this case however, there is no justification for a different approach to that followed for treatments for other heart failure conditions and that is unfair.

Finally, Pfizer's appeal is not, as suggested in your letter, based on an assertion that guidance is discriminatory simply because it does not recommend treatment for a condition affecting persons with a protected characteristic. Rather the issue is that, by inconsistent use of stopping rules based on assessment of symptoms using the NYHA classification (in circumstances where this determines whether access to treatment is recommended), the fact that forms of heart failure linked to protected characteristics are excluded from treatment as a result of these decisions is potentially discriminatory and heightens the requirement for adequate reasoning to explain the different approach adopted in different appraisals. That is absent in this case.

Ground 2

2.1 The Committee's approach to the economic modelling of patients who discontinue treatment with tafamidis during NYHA class 1,2 or 3 is internally inconsistent and disregards the trial data from the ATTR-ACT trial

Your preliminary view is noted.

2.2 The Committee's conclusion that there are "challenges" in making the diagnosis of ATTR-CM are not reasonable in the light of the available evidence

Your preliminary view is noted.

2.3 The Committee's statement indicating that all patients with suspected amyloidosis are referred to the National Amyloidosis Centre for testing is incorrect

You say in your letter that you are unclear why such an error by the Committee, regarding the need for referral to the NAC, would have resulted in an unreasonable recommendation.

However, it is Pfizer's case that a factual error is, by definition, unreasonable and the issue is not merely that evidence has moved on, but that the Committee has seemingly accepted this incorrect position rather than other evidence which conflicts with it. Furthermore, the error referenced in this point of appeal is relevant to the central conclusion by the Committee that diagnosis of ATTR-CM requires specialist input from the NAC and is slow, challenging and potentially uncertain (see paragraph 3.26 of the FAD). In contrast to this view, it is Pfizer's position that diagnosis of ATTR-CM is straightforward and may be made quickly, reliably and appropriately at many regional centres, consistent with experience in the EAMS.

It is unclear from the FAD the extent to which the Committee's error in relation to referral to the NAC contributed to the overall conclusion regarding delay and complexity of diagnosis (together with other matters with which Pfizer also disagrees) and that is not a matter which should be assumed at the initial scrutiny stage, particularly where the error involves a mistake of fact and one that goes to a key issue in this appraisal.

2.4 The Committee's suggestion that biomarkers could have been used as an alternative to NYHA classification to assess disease stage and who would benefit from treatment is unreasonable

You suggest that this point of appeal should not proceed to a hearing because "all the Committee is saying" is that, while it had concerns regarding use of the NYHA classification, it had no alternative measure to consider as the trial did not collect information on biomarkers.

You suggest that it is irrelevant to the outcome of the appraisal whether biomarkers were a suitable alternative measure to assess disease severity, as they were not in fact used.

We disagree. The Committee's conclusion that biomarkers would have been a suitable alternative to NYHA classification in measuring disease severity is unreasonable in circumstances where this is not a validated method and this unreasonable conclusion contributes to the Committee's inappropriate criticism of the ATTR-ACT trial and its decision that NYHA classification should not be used to determine disease severity.

Again it is impossible to know to what extent the Committee's criticism of the ATTR-ACT trial and mistaken belief that biomarkers should have been used as a measure for disease severity influenced the outcome of this appraisal. However the method used to assess disease severity is a central issue in this appraisal and the unreasonable conclusion that biomarkers should have been used to assess heart failure severity in the trial appears to have reinforced the Committee's incorrect conclusion that NYHA classification should not be used either in the trial or in clinical practice. In these circumstances, we do not agree that it is possible to conclude that the Committee's views on use of biomarkers had no influence on the outcome of this appraisal - indeed there are good grounds for reaching the opposite conclusion.

2.5 <u>The Committee's conclusion that it would be difficult for clinicians to implement a stopping rule for tafamidis does not reflect the available evidence</u>

Your preliminary view is noted.

2.6 <u>The Committee's conclusions regarding the time to diagnosis of ATTR-CM is unreasonable</u>

Your preliminary view is noted.

2.7 <u>The Committee's conclusion that tafamidis has no impact on awareness of ATTR-CM is inconsistent with its view that other products are increasing awareness</u>

You construe this point of appeal as being an argument based on an assumption of a linear relationship between introduction of a new treatment and increased awareness and say that you do not find the idea that every new treatment will lead to an increased awareness more or less plausible that awareness may be at or approaching a plateau. However this misunderstands the point made by Pfizer.

Firstly, the position is not that every new treatment will increase awareness of the condition but that the availability of the first and only licensed treatment will do so. The Committee concludes at paragraph 3.8 of the FAD that the availability of two treatments for ATTR polyneuropathy increased awareness of ATTR cardiomyopathy, even though they are not indicated for the treatment of cardiomyopathy, but declines to conclude that the availability of tafamidis, the first medicinal product to be authorised for the treatment of ATTR cardiomyopathy will increase awareness of the condition. This conclusion is unreasonable.

Secondly the attached timeline shows that, while scintigraphy DPD scanning had been available at a single centre, the NAC, since 2012 for the diagnosis of ATTR-CM, usage of this technique only became widespread with the availability of tafamidis for ATTR-CM through the EAMS and the approval of the cardiomyopathy indication by the European Commission. Therefore a survey conducted by the British Nuclear Cardiology Society showed that, in 2018,

85 tracer kits for the diagnosis of ATTR-CM were supplied to the UK, this figure increased to 145 kits in 2018. Furthermore, the number of centres conducting such tests had increased from one in 2012, to 21 centres in 2020, following the tafamidis EAMS. This increase in parallel with EAMS is, of course, entirely predictable. There is little purpose in diagnosing a condition if there are no treatments available and diagnosis will make little change to management. In contrast, the availability of an effective treatment is likely to prompt awareness and increased diagnosis. In the context of the data shown in the timeline, a conclusion that the availability will increase awareness of ATTR-CM is clearly correct and the refusal by the Committee to accept this is unreasonable.

2.8 The Committee's conclusions around the impact of tafamidis in reducing time to diagnosis as demonstrated through EAMS are not reasonable

Your preliminary view is noted.

2.9 The assertion that Pfizer failed to make use of longer-term data in its extrapolation of treatment effects is unreasonable.

You say in your letter that you do not see any connection between this point of appeal and the outcome of the appraisal and are therefore minded not to permit the point to proceed to a hearing.

However, the issue of long term benefits associated with treatment with tafamidis is a central issue in this appraisal and the appropriate modelling of overall survival based on the available trial data is an area of controversy (see e.g. paragraph 3.17 of the FAD). Any conclusion that the company has "failed" to disclose available longer term data is not only fundamentally incorrect, it is relevant to Pfizer's credibility and is also likely to have influenced the Committee in its interpretation of the data that were provided and Pfizer's proposed extrapolations.

It is of course difficult to correct the effect of that error and its impression on the Committee. Pfizer is however willing to proceed on the basis that the word "failure" is removed from the FAD, as suggested in your letter. Conversely, if that is not possible without further consideration by the Appraisal Committee, the matter should proceed to appeal.

Thank you for your consideration of the issues raised in this letter. We look forward to receiving your final views on the admissibility of our points of appeal.

Yours sincerely

[redacted], Pfizer UK

Enc: ID1531 timeline (Pfizer 23NOV2020).pptx