NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Sent by email to: [redacted]

[redacted]
[redacted]

Pfizer Limited,
Walton Oaks, Dorking Road,
Walton on the Hill,
Tadworth,
Surrey
KT20 7NS

9 November 2020

Dear [redacted]

Re: APPEAL AGAINST THE FINAL APPRAISAL DETERMINATION FOR TAFAMIDIS FOR TREATING TRANSTHYRETIN AMYLOIDOSIS WITH CARDIOMYOPATHY

Thank you for your letter of 30 October 2020, lodging Pfizer's appeal against the above Final Appraisal Document (FAD).

Introduction

The Institute's appeal procedures provide for an initial scrutiny of points that an appellant wishes to raise, to confirm that they are at least arguably within the permitted grounds of appeal ("valid"). The permitted grounds of appeal are:

- 1(a) NICE has failed to act fairly, or
- 1(b) NICE has exceeded powers;
- (2) the recommendation is unreasonable in the light of the evidence submitted to NICE

This letter sets out my initial view of the points of appeal you have raised: principally whether they fall within any of the grounds of appeal, or whether further clarification is required of any point. Only if I am satisfied that your points contain the necessary information and arguably fall within any one of the grounds will your appeal be referred to the Appeal Panel.

You have the opportunity to comment on this letter in order to elaborate on or clarify any of the points raised before I will make my final decision as to whether each appeal point should be referred on to the Appeal Panel.

Initial View

I assess each of your points in turn and then summarise the appeal points that I am presently minded to refer at the end of this letter.

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

I agree with your formulation that:

Adequate reasoning is a fundamental aspect of a fair and transparent procedure, so that a consultee such as Pfizer can engage with the process and understands in sufficient detail why its application has been unsuccessful and what it needs to do in order to achieve a positive result"

However I am not yet persuaded that the FAD, and the appraisal documents, which have to be read together in order to understand the committee's reasons, can be argued not to meet this test.

It seems to me that the committee is clearly aware of the algorithm, (I cannot see that they "reject" it?) summarises other evidence which it received, and gives a clear conclusion that there are still challenges in diagnosis. That conclusion may or may not be reasonable (and we return to that under ground two) but I cannot at present see an argument that evidence has been ignored or that reasoning is so absent as to be unfair?

I would not presently be minded to refer this point to an appeal panel.

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

Your argument here seems to sit firmly with ground 2. Misunderstanding or drawing the wrong conclusions from evidence can only go to the substance of the recommendation and not to the process followed to generate it. I agree this is a valid appeal point, but only under that ground.

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

A valid appeal point.

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

There are three elements to this point; that the approach is unexplained, that it is inconsistent with past appraisals (and thus calls for a higher degree of explanation) and that it is discriminatory.

As to the approach taken being unexplained it seems to me the committee does give reasons in the FAD. As I noted above the reasons may or may not be good and the conclusion drawn may or may not be reasonable but I cannot see that it can be said we are in the dark as to why the committee did not think rules based on the NYHA would be suitable.

As to consistency, you are clearly familiar with the appeal panel's past approach to expectations of consistency. There is a broad expectation of consistency of approach but this must not be overstated where each appraisal is likely to turn on very different evidence bases. I am 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, or would call for any reasoning over and above what would be required in any event.

As regards equalities, as I understand it your argument is that because this condition affects certain age groups and ethnicities more than others, then it would be discriminatory not to recommend it.

I am not minded to refer that argument on. Almost every condition will be more prevalent in one part of the population than another, whether defined by age, biological sex, ethnicity or otherwise. Put in its strongest form, the argument requires NICE to take a view on whether the NHS is appropriately balancing its resources across all conditions and in respect of all sections of the population. It is enough for present purposes to say that that is not part of NICE's remit.

Put in a weaker form the argument may be that a failure properly to appraise one treatment is discrimination against the population that would have benefited from that treatment, when compared with another population whose desired treatment was properly evaluated in a different appraisal. An appeal panel has considered this argument and has decided that while it may be logically possible to look at a defect in an appraisal in this way, it adds nothing to the analysis to do so unless the discrimination is a cause rather than a consequence of the defect in the appraisal.

Equality points which are suitable to be referred to an appeal panel are concerns that there is discrimination "within" an appraisal, for example that the position of a particular patient subgroup has been misunderstood or not taken into account. I do not think you are making such an allegation here.

I am not presently minded to refer any part of this ground to an appeal panel.

Ground 1b NICE has exceeded its powers

No grounds advanced.

Ground 2: the recommendation is unreasonable in the light of the evidence submitted to NICE

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

A valid appeal point.

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

A valid appeal point.

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

I am not yet clear why this error (assuming for present purposes it is an error) results in an unreasonable recommendation. It seems to me from the FAD that the Committee were concerned about misdiagnosis, and the sentence you refer to is a record of evidence given that should have reassured them that the risk of misdiagnosis was reduced (because an expert national centre was involved).

It may well be that things have moved on since that evidence was given and the necessary expertise now sits more widely within the NHS, but is the effect of that not simply that the committee should be even more reassured that diagnosis is in the hands of experts? I understand your concern is that the Committee may have thought accurate diagnosis was challenging, and you feel that it is not, but I don't see that this statement of itself suggests that the recommendation may be unreasonable?

I would not presently be minded to refer this point to an appeal panel.

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

I think this is a reference to the FAD reading:

"*The committee concluded that using the NYHA classification in ATTR-CM had limitations, but acknowledged that there was insufficient trial evidence available to consider an alternative. This was because cardiac markers, which could have been used to identify disease stage and who would benefit from treatment, were not measured frequently enough in the trial."*

At present I find it hard to see either how this statement is arguably unreasonable or that it makes the guidance unreasonable. All they are saying that they have concerns about the NYHA classifications, but they have no alternative to use in its place because of a lack of data. Even if the Committee are wrong about this and in fact no biomarkers exist that could be used to determine disease state, their error cannot have affected

the outcome. They seem to be saying we cannot use biomarkers because the data were not collected. You seem to be replying that in fact they could not use biomarkers because biomarkers are not suitable or do not exist. On either view, biomarkers were not used in the appraisal, so how can this difference of approach have produced unreasonable guidance?

I would not be minded to refer this point to an appeal panel.

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

A valid appeal point.

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

A valid appeal point.

2.7 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

I am not sure I see the arguable inconsistency that you claim, which seems to assume there must be a linear relationship between the introduction of a new treatment and increasing awareness. Why is it arguably irrational to conclude that awareness of a condition has increased in the past as a result of new treatments or diagnostic pathways, but will not increase further when a new medicine is introduced? I do not find the idea that every new treatment will lead to an increase in awareness any more or less plausible than the idea that awareness may be at or approaching a plateau and so new treatments will not make much difference.

I would not be minded to refer this point to an appeal panel.

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

A valid appeal point.

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

I do not see the connection between your assertion under this point and an arguably unreasonable recommendation. My concern is similar to the concern above under your point 2.4. For present purposes I am willing to assume the ERG meant that you could have used longer term data but did not, and that the Committee also believed that that this was the case. Your argument is that you used the data available to you and there was no "failure". If that is right I can see that the use of the word failure might need to be amended (although the committee were quoting a third party) but fundamentally the data submitted were the data that drove the appraisal. Even if the Committee erroneously thought there were other data that could have been submitted, that does not seem to me to support an argument that their treatment of the data that were submitted was unreasonable.

I would not be minded to refer this point to an appeal panel.

In respect of the points that I am not yet minded to refer you are entitled to submit further clarification and/or evidence to me within the next 10 working days, **no later than 23 November 2020,** and I will then give a final decision on the points to put before an appeal panel. For the points I am already content to refer on, an oral appeal will be held, although under current circumstances this is likely to be held remotely in part or in whole. Other appeals have been lodged and in due course the valid appeal points of each appellant will be shared to aid preparation for the appeal.

Many thanks

Yours sincerely

Tim Irish

Vice Chair

National Institute for Health and Care Excellence