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Dear

Appeal against Final Appraisal Determination (FAD): Pirfenidone for treating idiopathic pulmonary fibrosis (Review of TA 282).

Thank you for your letter of 19 October providing additional comment on my initial scrutiny of your Client's appeal. This is my final decision on initial scrutiny.

Ground 1 (a)

1.1 In failing to consider the totality of data in respect of 'adults with mild to moderate idiopathic fibrosis' (which is both the full licensed indication and the relevant population as identified in the final scope), and in particular determining that 'the subgroup with a FVC between 80% and 90% predicted was the relevant population for decision making (para 4.5 FAD) the Committee acted contrary to policy and procedures (in particular paragraphs 3.2.2, 5.1.4, 5.10 and 6.2.18 of the Methods guide) with inadequate reasons and unfairly.

Already accepted as valid.

1.2 The identification of the 80%-90% sub-group at such a late stage of the process, with no consultation or opportunity for relevant evidence or critiquing of evidence to be submitted, was in breach of NICE's obligations of consultation, disclosure and transparency, and contrary to NICE's policy and procedures (in particular paras 3.3.9 and 3.7.31 of the Guide to the processes of technology appraisal and para 3.1.1 of the Methods Guide).

I agree that if the law requires a higher standard of transparency than the Methods Guide then the law prevails.

Equally, as you will be aware, fairness in this or any other public law setting is context dependent. I do not think the Eisai case can be taken to have laid down a general rule for every question of fairness that may arise in any appraisal: you will know it concerned access to the economic model that was at the heart of that particular appraisal.

The Methods Guide is the product of consultation with stakeholders and it or its predecessors has been in use for many years essentially without challenge. It is reasonable to be guided by its terms as a generally accepted statement of what would be fair in the circumstances, but I am alive to the point that it may not be definitive.

I would also observe that an appraisal must be fair and transparent when looked at overall. That is particularly relevant as your point here (in contrast to point 1.1) is essentially one of timing. In ground 1.1 you challenge the decision to look at subgroups at all. Here in contrast you complain that a particular subgroup was introduced unfairly. (In passing, this distinction is why I would not agree that there would be any inconsistency in allowing point 1.1 to proceed, and not point 1.2.)

It is significant that consideration of the 80-90% group was in the context of considering material gathered in consultation, as can be seen from the slide deck at the committee meeting. The ACD contained a discussion of subgroups (not, to be

clear, the 80-90% subgroup but an 80-100% subgroup.) Your client responded at some length on the question of subgroups, and those comments were considered in preparing the FAD. Whether as a result of those comments and/or a more general consideration of all the evidence when finalising its conclusions, the committee eventually worked with an 80-90% subgroup and not an 80-100% subgroup (although it took account of the evidence for that subgroup see FAD 4.9-4.10).

I am firmly of the view that this timing point is not arguably an unfair process. An above 80% subgroup was in play throughout. Your client made comments on that and had submitted data about it. That material was all considered. The final subgroup considered was 80-90% and not 80-100% but it is inherent in any consultation process that the proposal consulted on may change as a result of consultation and consideration. In my judgement the key point is that an above 80% group was identified and consulted on, and that the change from 80-100% to 80-90% was not so significant as to render the process unfair. Whether looked at through the Methods Guide or through the Eisai case I do not think this degree of change approaches the level at which your client can complain of an unfairness with any prospect of success.

Therefore I still do not consider this a valid appeal point.

1.3 The Committee's assessment of clinical effectiveness is internally contradictory, inadequately reasoned and unfair and is contrary to its policies and procedures (in particular para 6.1.9 of the Methods guide).

I do not agree that there is an inconsistency between considering that it is arguable that a judgement is perverse and that it is not arguable that the judgement was reached as a result of a procedural unfairness. As I understand it the proposition that every unreasonable judgement must also be a procedurally unfair one is not generally held, and the same must be true for arguably unreasonable judgements being arguably unfair. The grounds of appeal are distinct.

I do not accept that there is a legal requirement for a committee to provide reasons for every point on which it disagreed with an ERG (or, presumably, a manufacturer).

In my judgement the Servier case turns on the fact that the body from which NICE apparently departed was the EMA exercising its regulatory function. I do not accept that Servier is any authority that disagreement with an ERG calls for any particular level of reasoning. In my judgement the test is more general: does the guidance contain sufficient reasoning on the main points that the conclusions can be understood and adequately engaged with, or (which I take to have the same result) is the guidance sufficiently reasoned that it can indeed take effect as guidance to the educated reader, rather than as instruction.

Like you I will not repeat the points made in the initial exchange of correspondence. As to the point that an absence of evidence that there is a difference between groups does not explain a finding that there is likely to be such a difference, the committee does not say that it does. They say from the evidence presented to them pirfenidone is likely to be less effective in patients with FVC > 80%. While you have focused on the interaction tests (which as I understand it fail to rule out the Committee's hypothesis, and whether that can be said to "support" the hypothesis may be a matter of debate), you have to read the whole of paragraph 4.9 and indeed the FAD. For example they also refer to treatment effects noting that in the CAPACITY 1 trial the treatment effect for FVC > 80% was not statistically significant. Whether these reasons are correct is not for me to say, but I cannot see that it can be said that they are absent.

As to the ability to form a judgement on the FAD, in my view it is clear that the committee concluded that certainty was not possible but that the benefit of treatment for patients with FVC >80% was likely to be less than for patients with FVC 50-80%. I therefore do not understand why the reader would be unclear whether it is possible to form a view as to treatment effect, they do form such a view, albeit tentatively. Not least because the view is tentative I would have thought the informed reader would infer a lack of statistically robust evidence to the contrary, and would be alert that if he/she was aware of such evidence or reviewed the appraisal's supporting papers and concluded that the Committee had been unduly critical of it, then he/she should take that into account when exercising judgement informed by the guidance. Hence the reasoning seems adequate.

The worst that can be said is that the table summarising the reasoning has not fully captured it and has been too favourable to the treatment, which is something that the Guidance Executive can and should consider if the guidance was to be published in its current form.

Therefore I still do not consider this a valid appeal point.

Ground 2

2.1 Failing to consider the totality of data in respect of adults with mild to moderate idiopathic fibrosis (which is both the full licensed population and the relevant population in the Final Scope) and in particular determining that the 'sub group of people with an FVC between 80% and 90% predicted was the relevant population for decision making' (para 4.5 of the FAD), was perverse.

Already accepted as valid.

2.2 Identifying the 80%-90% group at such a late stage of the process with no consultation and no opportunity for relevant evidence or critiquing of evidence to be submitted, was perverse.

I understand the distinction between the process of gathering evidence and the defensibility of the conclusions drawn from it. However I noted in commenting on your point 1.3 above that one cannot simply read across from an arguable perversity to an arguable procedural defect, and the same is true in reverse.

You have presented no reason to suppose that the use of the 80-90% group was perverse other than the procedural points discussed and rejected above. For clarity, I have also considered those points as evidence of perversity, and I reject them under that heading. It seems to me that adopting an 80-90% subgroup on the basis that the evidence in patients with an FTC of 90-100% was lacking was well within the reasonable approaches open to a committee, albeit other reasonable approaches also exist. (I say that only on the assumption that it was open to the committee to

look at subgroups with FTC > 80% at all, which of course is an issue that the appeal panel will be looking at. If you succeed on that point the question does not arise.)

Therefore I still do not consider this a valid appeal point.

2.3 The Committee's assessment of clinical effectiveness was perverse.

Already accepted as valid.

This is the final decision on initial scrutiny. The valid appeal points are: 1.1, 2.1, 2.3.

Yours sincerely

Andy McKeon
Vice-chair
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