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Our Ref: HB3/HB3/60847-00005/57105218 v4

Your Ref: TA282

19 October 2016

Dear Mr McKeon

Appeal against Final Appraisal Determination - Pirfenidone for treating idiopathic pulmonary fibrosis (Review of TA282, dated September 2016)

Thank you for your initial scrutiny letter of 10 October 2016 confirming that Roche's appeal will be passed to the appeal panel for consideration; we have since been informed that the oral hearing will take place on 2 December 2016. While the appellant is grateful that its grounds 1.1(a), 2.1 and 2.3 have been considered valid appeal points, it wishes to respond in relation to the grounds which you are not minded to regard as valid, as set out below.

Ground 1.2(a): The identification of the 80%- 90% subgroup 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 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)

As to the relevant legal test, the appellant respectfully relies on *R (Eisai) v NICE* [2008] EWCA Civ 438, namely that NICE's process requires a "*very high degree of transparency*" with "*an exceptional degree of disclosure and consultation*". Whilst the appellant does say that para 3.7.31 was breached as well, if there were to be an inconsistency between para 3.7.31 and the public law requirements established by *Eisai*, then of course *Eisai* would prevail.

With this in mind, the appellant respectfully submits that simply working through para 3.7.31 (asking whether e.g. the recommendation had changed between the ACD and the FAD) is not the proper approach, or at least only establishes whether para 3.7.31 has been breached. Rather, the Vice Chair should ask himself whether the Appraisal Committee also complied with its very high and exceptional obligations of consultation, disclosure and transparency.

The appellant says that the Appraisal Committee did not so comply. It relies on its submissions in its Appeal Letter in support (and does not repeat them here). Responding to the Initial Scrutiny letter, the appellant respectfully submits that the reasoning in that letter focuses entirely on the 90% upper limit for the group, and fails to grapple with the combination of that upper limit with the lower limit of 80%. In particular:

- As to "*However, the ACD noted that the ASCEND trial (referred to in the scope as one of the prime reasons for the review) excluded patients with a predictive FVC greater than 90%*": the appellant fully accepts that the ASCEND trial related to the group 50%-90%.

- As to "*and the ERG noted that the ICERs for the group above 80% predicted FVC would have been higher had more people with predicted FVC of over 90% been included (and therefore less favourable to the company's case)*": as set out in para (d) under ground 1.1(a) of the Appeal Letter, there is no statistically significant evidence to support a conclusion that individuals with greater predicted FVC have better underlying risk. Moreover, because there is no available data for the group 80%-90%, in fact the data related to the group >80% (as is pointed out in the second example of unfairness under ground 1.2(a) in the Appeal Letter). Accordingly, the ERG's comment is inapplicable (and, if anything, demonstrates the irrationality of the group 80%-90%).

- As to "*the FAD itself also notes that the company had presented some data with an upper limit of 90% predicted FVC because most of the data was supported by patients within that limit*"; again, the appellant accepts that the ASCEND trial related to the group 50%-90% and so the data largely relates to that group.

The reasoning in the initial scrutiny letter therefore fails, with respect, to address the combination of the 90% upper limit with the 80% lower limit, i.e. the creation of the subgroup. This was novel and, unsupported by evidence.

As to unfairness, in particular the statement in the initial scrutiny letter that "*I struggle to see how it was unfair for the Committee to focus in the FAD on the 80-90% subgroup*", the appellant repeats its examples set out in its Appeal Letter. However, it further emphasises that, if the Appraisal Committee had identified this subgroup when it should have done, (i.e. at ACD stage) as part of its transparent dialogue with the appellant, the appellant would have been able to make the points raised at ground 1.1(a) and 2.1. These objections, which have already been acknowledged as a valid appeal point by the Vice Chair, should have been taken into account at the proper time. Moreover, they might have led to a substantively better decision (not one which is perverse, as has been found to be a valid appeal point in respect of ground 2.3). This is precisely the function of consultation, and of a transparent and open dialogue, with which

standards the Appraisal Committee failed to comply. Accordingly the appellant respectfully asks that it be given the opportunity to pursue this ground of appeal.

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

The appellant notes that its Ground 2.3 ("*The Committee's assessment of clinical effectiveness was perverse*") has been considered a valid appeal point, however Ground 1.3(a) has not; it is unclear how the Vice Chair could consider the assessment of clinical effectiveness to be potentially perverse without being potentially internally contradictory, inadequately reasoned, unfair, or contrary to NICE's policies or procedures. Moreover, since the appellant's submissions under Ground 2.3 will necessarily involve consideration of these arguments (amongst others), it asks that it be allowed to pursue them under Ground 1.3(a). There must otherwise be a risk that the appellant might succeed in a finding of procedural breach as part of Ground 2.3, but be left (if this does not amount to perversity) with no remedy.

Turning to the reasoning in the initial scrutiny letter, the appellant is mindful not to repeat points already made in its Appeal Letter (for example, as to the need to justify taking a different view to that taken by the ERG and which is surprising on its face). With that in mind, and focussing on the initial scrutiny letter:

- The appellant does not consider that paragraph 4.9 of the FAD provides an adequate explanation for the conclusions in paragraph 4.10. In particular, a finding that there is an absence of conclusive evidence to show that there is no difference in treatment effect (para 4.9) does not explain a finding that there is in fact likely to be such a difference (para 4.10).

- As to internal inconsistency, the appellant adopts the language of the initial scrutiny letter: what is the link between *"uncertainties in the evidence"* and the ability to form a "*qualified judgment*"? It is submitted that a reader would be left entirely unclear whether there was a dearth of statistically robust evidence, or whether to the contrary it was possible to form a view as to treatment effect.

Why this matters is, of course, that the lack of statistically robust evidence is attributable to the (wrongful) identification of the 80%-90% subgroup. This should have led to the abandonment of that subgroup, rather than to the casting of unsubstantiated aspersions as to treatment effect. This does significant unfairness to the appellant (and indeed to the reputation of pirfenidone) and the appellant asks for the opportunity to pursue this ground of appeal.

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

Ground 2.2 Identifying the 80%- 90% subgroup 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.

To treat this complaint as purely concerning the "*possible unfairness of the process*" is, with respect, to fail to recognise the substantive function of the consultation and the gathering of evidence. This is clearly a

Ground 2 perversity point as well as Ground 1 procedural unfairness, as the appellant's position is that the 80% - 90% subgroup should not have been used and was perverse, which the Vice Chair has already considered to raise valid appeal points. Accordingly, NICE's decision to identify and base its decision on such a subgroup is similarly a potentially perverse decision, and the appellant asks for the opportunity to pursue it as a ground of appeal.

Conclusion

The Appellant requests that the Vice Chair consider the comments made above before making a final decision. We understand from the Guide to the technology appraisal and highly specialised technologies appeal process that we will receive the final scrutiny letter within 5 working days of receipt of this letter.

Yours sincerely

cc: