fieldfisher

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

5th Floor
Free Trade Exchange
37 Peter Street
Manchester M2 5GB

T +44 (0)161 835 8010
F +44 (0)161 835 8015
E info@fieldfisher.com

www.fieldfisher.com

By Email (appeals@nice.org.uk)

Our Ref: SLE/HB3/60847-00005/56948080 v1
Your Ref: TA282

30 September 2016

Dear Mr McKeon

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

This letter sets out the appeal by Roche Products Limited ("the company" or "the appellant") in respect of the Final Appraisal Determination ("FAD") for pirfenidone (commercially known as Esbriet) for treating idiopathic pulmonary fibrosis ("IPF") (Review of TA282, dated September 2016). The grounds of appeal are:

- Ground 1(a): In making the assessment that preceded the recommendation, NICE has failed to act fairly;
- Ground 2: The recommendation is unreasonable in light of the evidence to NICE.

EXECUTIVE SUMMARY

This appeal relates to the recommendation that "*pirfenidone is recommended as an option for treating idiopathic pulmonary fibrosis in adults only if the person has a forced vital capacity (FVC) between 50% and 80% predicted*". For the avoidance of doubt, no appeal is brought in respect of either of the two other limbs to the recommendation, namely that "*the company provides pirfenidone with the discount agreed on the patient access scheme" and that "treatment is stopped if there is evidence of disease progression (an absolute decline of 10% or more in predicted FVC within any 12-month period)*".

The appellant's appeal under Ground 1(a) - namely that, in making the assessment that preceded the recommendation, NICE failed to act fairly - comprises three points of appeal:

- The first point of appeal under Ground 1(a) is that "*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 in determining that "the subgroup of people with an FVC between 80% and 90% predicted was the relevant population for decision-making" (para 4.4, FAD), the Committee acted contrary to policy and procedures (in particular paragraph 3.2.2, 5.1.4, 5.10 and 6.2.18 of the Methods Guide), with inadequate reasons and unfairly*".

- The second point of appeal under Ground 1(a) is that "*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 paragraphs 3.3.9 and 3.7.31 of the Guide to the processes of technology appraisal and paragraph 3.1.1 of the Methods Guide)*"

- The third point of appeal under Ground 1(a) is that "*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 appeals under Ground 2 by reference to the same detailed arguments set out in respect of Ground 1(a), which demonstrate that the evidence before the Committee was such that their recommendation was unreasonable and perverse.

INTRODUCTION

The appellant is responsible for the UK supply of pirfenidone, which received marketing authorisation from the European Medicines Agency in February 2011, for the treatment of mild to moderate IPF.

PROCEDURAL HISTORY OF THE APPRAISAL

Pirfenidone was originally recommended by NICE as an option for the treatment of IPF in TA282 in March 2013 if the person has a forced vital capacity (FVC) between 50% and 80% predicted and the manufacturer provides pirfenidone with the discount agreed in the patient access scheme. NICE also recommended that treatment should be discontinued if there is evidence of disease progression (a decline in per cent predicted FVC of 10% or more within any 12 month period). However, the Appraisal Committee stated that the guidance would be reviewed within six months of the publication of the ASCEND study, which was expected to provide further information on the efficacy of pirfenidone.

In 2014 NICE proposed that TA282 should be transferred to the 'static guidance list' on the basis that, whilst the ASCEND study had demonstrated the clinical effectiveness of pirfenidone on patients with FVC up to 90% predicted, this was believed to only impact on a very small number of patients. Responses received from stakeholders indicated that a significantly larger number of patients with IPF have an FVC

greater than 80% and therefore would potentially stand to benefit from pirfenidone. After a consideration of all of the comments NICE decided in October 2014 that TA282 should be updated.

The subsequent history of the appraisal is summarised as follows:

- 23 December 2015: Final Scope issued and matrix issued, setting out the remit for the appraisal.
- 5 May 2016: The first meeting of the Appraisal Committee to consider the proposed changes to TA282. The appellant is represented by and a Health Economist employed by BresMed.
- 26 May 2016: Appraisal Consultation Document ("ACD") sent to registered consultees and commentators in confidence.
- 3 June 2016: ACD published.
- 24 June 2016: The appellant and other registered consultees and commentators submit their responses to the ACD.
- 4 August 2016: The second meeting of the Appraisal Committee to consider the proposed changes to TA282. The appellant is again represented by and
- 9 September 2016: Final Appraisal Determination ("FAD") issued to Roche and released publically one week later on 16 September 2016.

OVERVIEW OF THE TECHNOLOGY

IPF is a chronic, progressive, and fatal lung disease that is characterised by irreversible loss of lung function. Early treatment to delay progression should, therefore, be an important goal for the management of the condition. Much clinical opinion strongly advocates for earlier access to treatments and so expanding the population of those who can receive pirfenidone to treat IPF is therefore a primary objective.

Pirfenidone is an oral immunosuppressant with anti-inflammatory and antifibrotic effects. It has a market authorisation in the UK for treating mild to moderate IPF in adults. The summary of product characteristics states that the very common adverse reactions (affecting 1 in 10 or more people) associated with using pirfenidone are nausea, rash, diarrhoea, fatigue, dyspepsia, anorexia, headache and photosensitivity reactions. The recommended dosage of pirfenidone is three 267 mg capsules 3 times daily (a total of 2,403 mg per day).

GROUNDS OF APPEAL

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

Ground 1.1(a): 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 in determining that "*the subgroup of people with an 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.

Pirfenidone is licensed for adults with mild to moderate IPF. This was identified in the Final Scope in December 2015 as the relevant population for the present review. This formed the focus for the appellant's lengthy submissions and participation in the consultation process (which is fundamental to the quality of NICE's decision-making and the maintenance of NICE's high standards of transparency and disclosure).

The Committee failed to consider the totality of the data in respect of the full licensed population as identified in the Final Scope[1] (as the appellant says it should have done). Instead, it identified a patient subgroup on the basis of 80% to 90% FVC predicted. The identification of the subgroup of people with an FVC between 80% and 90% predicted was contrary to para 5.10 of the Guide to the methods of technology appraisal ("the Methods Guide"). In particular, there are no "*known, biologically plausible mechanisms, social characteristics or other clearly justified factors*" to justify the subgroup (para 5.10 of the Methods Guide). To the contrary, the subgroup is unjustified. In particular (but non-exhaustively):

(a) The Committee acknowledged that 80% is an arbitrary line (FAD: para 4.5, first bullet).

(b) The Committee relied on its understanding that 80% was used in clinical practice (FAD: para 4.5, first bullet) without acknowledging the role that the extant guidance TA282 will have had in establishing such clinical practice (since it uses the 80% dividing line for treatment). It thereby illegitimately incorporated the original TA282 into the review exercise, significantly predetermining the outcome.

(c) The Committee acknowledged that it is not possible to identify subgroups in accordance with any known biologically plausible mechanisms for identifying subgroups (FAD: para 4.5, second bullet). It says "*but [it] noted that the company stated in its response to the appraisal consultation document that idiopathic pulmonary fibrosis is 'a complex disease that is not yet fully understood for subgroups'*". From the drafting, it therefore appears that the Committee believed that such a lack of evidence justified their approach of going on to define subgroups. Any such belief would be misplaced (and indeed the appellant clearly rejected the appropriateness of any subgroup analysis in its comments on the ACD (see both the cover letter dated 24 June 2016, and pages 4-10 of the submissions) and during the August Appraisal Committee meeting[2]). The Methods

[1] While the possibility of subgroup analysis was raised in the Final Scope, such analysis was said to be only "if evidence allows". The evidence did not support such analysis, as is apparent from the fact that the posited subgroup does not meet the requirements of paragraph 5.10 of the Methods Guide.

[2] On an allied point, whilst the Committee's statement that "*It recognised that the company had presented analysis with different subgroups of people with idiopathic pulmonary fibrosis*" (FAD: para 4.4) is true so far as it goes, this statement is liable to mislead (since it fails to recognise that the appellant submitted that

Guide requires that there be some evidence in support of subgroups; it is not enough to rely on an absence of evidence against subgroups.

(d) The Committee essentially relied on a non-significant higher death rate (and higher rate of decline) for those with 50%-80% FVC compared to those with greater than 80% FVC (FAD: para 4.5, third bullet). This was wrong for two reasons. Firstly, IPF is an orphan condition (ie it is rare, affecting fewer than 5 in 10,000 people) and the number of patients available for inclusion in clinical trial programmes is so small that particular care must be taken over whether the available evidence is statistically robust (as required inter alia by para 3.2.2 of the Methods Guide[3]). In the appellant's submission, there is no statistically-significant evidence to support a conclusion that individuals with greater than 80% FVC have better underlying risk (ie are less likely to die) than those with less than 80% FVC. Secondly, even if such a premise were justified on the evidence (or even if it were scientifically justified simply to take this point as intuitively likely to be correct), it would be an illegitimate basis for the drawing of a line between subgroups. It may presumably frequently be true that individuals at the less severe end of a cohort are (to put it bluntly) less likely to die, and so more costly to treat. However, this is no basis for drawing a line through that cohort and dividing it into subgroups (with the less severe subgroup thereby disentitled to the technology, even though the technology is clinically and cost-effective across the cohort taken as a whole). With no principle underpinning such a line, where it is drawn is fundamentally arbitrary. This is a dangerous - and unfair – precedent to set, with its obvious potential ramifications for other cases. It is a misuse of, and in breach of, the concept of subgroups as endorsed in para 5.10 of the Methods Guide, in which there must be a concrete difference between the subgroups. It is further in breach of para 6.2.18 of the Methods Guide, which requires that the Committee "*may recommend the use of an intervention for subgroups of the population only when there is clear evidence that the characteristics defining the subgroup influence the effectiveness and/or cost effectiveness of the intervention*". Drawing a line arbitrarily through a group which contains a sliding scale of illness is a world away from distinguishing between two distinct, pre-existing and objectively determinable subgroups.

(e) The Committee wrongly took the question which it believed itself to be considering in the review (namely whether the recommendation should be increased to include individuals with >80% FVC) as determinative of the existence of a corresponding subgroup (namely individuals with >80% FVC). This error is apparent from its statement that "*given that one of the objectives of the review was to consider whether pirfenidone was cost effective in people with an FVC above 80% predicted, the committee agreed that the most accurate way to do this would be to consider the*

---

this analysis did not support a subgroups approach). Either the Committee misunderstood the appellant's submissions, or the FAD is (at best) poorly expressed here.

[3] Para 3.2.2 provides that, when dealing with small sample sizes, "*analyses should be explicit about the limitations of the evidence, and attempts to overcome these, and quantify as fully as possible how the limitations of the data are reflected in the uncertainty in the results of the analysis.*"

cost effectiveness in people with an FVC above 80%, rather than for the whole population" (FAD: para 4.5, third bullet). The Committee therefore translated the upper boundary set by the extant guidance (TA282) into being the lower boundary of a subgroup. This is in breach of para 5.10 of the Methods Guide and is scientifically illegitimate. Moreover, if this were the right approach, it should have been identified at the earliest stages of the review exercise (since it simply flows directly from the scope of the review itself, rather than from any evidence or submissions). Failure to do so was a further procedural impropriety and caused further unfairness.[4]

(f) The Committee relied on the availability of data relating to the group 50%-90% as a basis for setting an upper boundary of 90% (FAD: para 4.5, fourth bullet, and conclusion). Had the Committee stopped there, and considered the group 50%-90% as being the appropriate population on the basis of available evidence, this would have been entirely proper. However, the Committee went on to combine that upper limit of 90% with the lower limit of 80%. This fatally subverts the Committee's reasoning: whilst there is readily available data and analysis for the group 50%-90%, there was no such data and analysis for the group 80%-90%. The identification of this subgroup using the justification of available evidence is therefore (and in any event) in breach of the guidance.

The appellant also places reliance on the remainder of its grounds of appeal (both the further points of appeal under Ground 1(a); and the fact that the recommendation is perverse, as set out under Ground 2) as further evidence of the unfairness, and illegitimacy, of the Committee's approach to subgroups.

In conclusion, 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 in determining that "*the subgroup of people with an 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 paragraph 5.10 of the Guide to the methods of technology appraisal), with inadequate reasons and unfairly.

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)

The subgroup of 80%-90% FVC appeared for the very first time in the FAD. To the appellant's knowledge, this subgroup had never been identified by the Committee previously. By way of example, even the slides setting out the Chair's presentation at the 2nd Appraisal Committee meeting on 4 August 2016 give the following options for the relevant population "*>50% (no upper limit) combining subgroups, 50%-90%*

[4] See also para 5.1.4 of the Methods Guide, which expressly says that "*the decision problem* [for cost effectiveness] *should be consistent with the Institute's scope for appraisal; any differences must be justified*". There was no such justification in the present case.

reflecting the evidence, and ≥ 80% the subgroup not included in existing guidance" (p.5); similarly it set out three options for the relevant population (>50, >80 and 50 to 90) on p.35. While subgroups were discussed in emails between the appellant and NICE of around 14 June 2016, again the 80%-90% FVC subgroup was not discussed.

The emergence of the 80-90% population was such a fundamental change that it was conspicuously unfair for the Committee not to consult on it. Whether or not it was appropriate to employ this subgroup was a matter of critical significance for the outcome of this review. Such further consultation would be required, as a matter of public law, of any consultation; but is all the more necessary in the present context. As the Court of Appeal recognised in *R(Eisai) v NICE [2008]* EWCA Civ 438, in conducting a technology appraisal NICE is "*discharging an important public function which engages a strong public interest*" and so there is a "*need for a very high degree of transparency in the process, with an exceptional degree of disclosure and consultation*" (para 35). Failure to reconsult was also in breach of para 3.7.31 of the Guide to the processes of technology appraisal.

This is not simply an academic complaint. Such consultation would have given the opportunity for interested parties (in particular the appellant) to have given their view on the appropriateness and relevance of that subgroup, and moreover to present their own evidence and/or to comment on and critique evidence put forward by others.

By way of two examples of this unfairness:

- Firstly, in the FAD the Committee stated "*It noted that the analysis presented by the company included people with FVC above 80% predicted, and it had not been presented with cost-effectiveness results for the specific group of people with an FVC between 80% and 90% predicted*" (section 4.18, our emphasis).[5] The fact that it had "not been presented" with such results is no surprise, given that (a) the Committee had never asked the appellant to provide cost-effectiveness results for the specific group of people with an FVC between 80% and 90% predicted, and (b) the FAD was the first time that such a sub-group was identified by the Committee. If given the opportunity, the appellant would have explained that the model relies on mortality data, and that there were only 11 deaths in the 80%-90% subgroup (across both placebo and pirfenidone) and so there can be no robust analysis of the data on any standard approach. This in itself would have demonstrated that the subgroup of 80%-90% was not appropriate.

- Secondly, it appears that the ICERs in para 4.18 of the FAD were in fact calculated using data which related to the group >80% (with no upper 90% limit – and therefore (using NICE's premise as to underlying risk) generating less favourable ICERs), but this understanding is only based on the appellant's attempts to reach those same figures following the FAD. The appellant had never

[5] See a similar statement in para 4.14: "*The committee noted that, in its response to the appraisal consultation document, the company did not provide new clinical evidence but did provide revised analyses with…[a] new subgroup with an FVC between 50% and 90% predicted. The committee considered the cost effectiveness of pirfenidone for the group with FVC between 80 to 90% predicted as more relevant (see sections 4.5 and 4.18 for the discussion about the subgroup).*"

been given a chance to check, review or otherwise critique those ICER figures before the FAD. Following receipt of the FAD, the appellant requested the relevant model (with NICE's preferred assumptions programmed into it), and NICE supplied it on 20 September 2016. Given the centrality of the ICERs to the decision, the appellant should have been given the chance to comment on and critique the model earlier in the process (as per *R (Bristol-Myers Squibb) v NICE* [2009] EWHC 2722). This was also required under NICE policies and procedures (see, by analogy, the requirements of para 3.3.9 of the Process Guide, under which NICE must make analyses which cannot be easily replicated by the company, available to the company at the fact check stage). Indeed, this would have given the appellant the opportunity not only to comment on the generation of ICERs for subgroups (and in particular whether any such figures can be statistically robust), but also to use that same model to generate ICERs for the totality of the population.[6]

Accordingly, in failing to comply with its obligations of consultation, transparency and disclosure (and its procedure and policy, such as para 3.7.31), the Committee also failed to marshal the evidence on which its ultimate conclusions should have been based. This was in breach of its own policies and procedures (for example, see para 3.1.1 of the Guide to the methods of technology appraisal: "*it is essential that the evidence and analysis, and their interpretation, are of the highest standards and are transparent*") and was unfair.

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 Committee's treatment of clinical effectiveness is internally contradictory, unfair and inadequately reasoned. This is also contrary to its policies and procedures (in particular paragraph 6.1.9 of the Methods Guide; "*The reasoning for the Committee's decision will be explained, with reference to the factors that have been taken into account*"). In particular:

- The ERG concluded that there was no evidence in support of a difference in clinical effectiveness between a subgroup of 50-80% and >80% (see eg p.234 of its report presented to the Appraisal Committee meeting of May 2016). In its second submission, it summarised this as "*the approach taken by ERG in their original report was consistent with the lack of statistical evidence to support a difference in clinical effectiveness*" (p.6). But the Committee apparently reached a different view of the evidence when it concludes that pirfenidone is "*more likely to be less effective*" in the >80% group than in the lower group (FAD: para 4.10) without explanation as to why it disagreed with the ERG. As per the Court of Appeal in *Servier v NICE* [2010] EWCA Civ 346, this sort of conclusion

[6] Indeed, the appellant has now plugged the data for the 50%-90% FVC predicted group into the model used in the FAD, generating ICERs of £25.9K to £29K. This is exactly the sort of exercise which the appellant would have been able to undertake if NICE had complied with its obligations of consultation, disclosure and transparency.

(which departs from the ERG and is surprising on its face) should contain proper adequate reasoning in support. Such reasoning is lacking in the present case, and this is unfair. In particular, the Committee's apparent reliance on a lack of evidence to "*conclusively mean that there is no difference in treatment effect between subgroups*" (FAD: para 4.9, second bullet point) to support a view that there is such a difference is surprising and would require significant explanation.

- Furthermore, whilst the Committee correctly noted that "*none of the studies were designed to specifically determine the effectiveness of pirfenidone in people with FVC between 80% and 90% predicted*" (FAD: para 4.10), it should have recognised that this is indicative of the inappropriateness of the subgroup. This is further evidence of the unfairness of assessing clinical effectiveness in respect of such a subgroup.

Moreover, the FAD is internally inconsistent in respect of clinical effectiveness:

- The section in paras 4.9-4.10 appears[7] to conclude that pirfenidone has less clinical effectiveness in the group >80. It says that it is "*more likely to be less effective*" in this group.

- In contrast, in the "summary of appraisal committee recommendations" it is simply stated that "*it is not clear whether pirfenidone was more, less or equally effective in the group with FVC above 80% predicted than in the group with FVC of 80% or less predicted*" (p. 21).

- Whereas, in the cost-effectiveness section, the FAD says "*the committee recalled that it had not seen robust analyses showing that pirfenidone reduces mortality or consistently reduced the decline in percent predicted FVC, in people with an FVC between 80% and 90% predicted (see sections 4.9 and 4.10)*" (FAD: para 4.18).

This internal inconsistency is unfair and symptomatic of inadequate reasoning.

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

Ground 2.1(a): 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 of people with an FVC between 80% and 90% predicted was the relevant population for decision-making" (para 4.5, FAD), was perverse.

---

[7] The appellant has also raised a point of factual/typographical clarification in respect of the first two bullet points in para 4.10 FAD (by way of email sent separately to TACommB@nice.org.uk). These two bullet points presently read "*pirfenidone may reduce disease progression, although the results from these analyses were not robust*" and "*there was no statistically significant reduction in mortality with pirfenidone compared with placebo*". Both of these are presumably intended only to refer to the group >80%, but on their face they read as if they might apply across the board. The appellant has therefore suggested that, in order to capture the Committee's intended meaning more precisely, words such as "*for people with FVC >80% predicted*" should therefore be inserted into these bullet points.

The points set out in 1.1(a) above also demonstrate that the guidance cannot reasonably be justified in the light of the evidence submitted, in that there is no basis for preferring subgroups over the a consideration of the totality of the data, still less a subgroup of 80%-90%. The Committee's approach was one which no reasonable public body would have taken.[8] Indeed, the reasons put forward by the Committee are on their face perverse (for example, the Committee justified the 90% upper limit by reference to available data, when it acknowledges elsewhere that there is no available data (either in respect of clinical or cost effectiveness) in respect of the 80%-90% subgroup). In the circumstances set out under 1.1(a) above, the Committee's recommendation was unreasonable.

Ground 2.2(a): 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.

The points set out in 1.2(a) above also demonstrate that the guidance cannot reasonably be justified in the light of the evidence submitted. By way of example, the Committee perversely failed to give any notice of, or seek any relevant evidence in respect of, the subgroup which it identified as the relevant population for decision-making (namely the 80%-90% group). In the circumstances set out under 1.2(a) above, the Committee's recommendation was unreasonable.

Ground 2.3(a): The Committee's assessment of clinical effectiveness was perverse.

The points set out in 1.3(a) above further demonstrate that the guidance cannot reasonably be justified in the light of the evidence submitted. The Committee's approach to the evidence was perverse. For example, in the face of no evidence that there was any difference between those <80% and those >80%, the Committee concluded that there was in fact such a difference. This was perverse. In the circumstances set out under 1.3(a) above, the Committee's recommendation was unreasonable.

Conclusion

For the reasons set out above, the appellant believes that, in making the assessment that preceded the recommendation, NICE failed to act fairly and exceeded its power; and that its recommendation that pirfenidone only be used if a person has a FVC of between 50%-80% FVC predicted is unreasonable in light of the evidence submitted to NICE.

The appellant requests an oral hearing for the determination of this appeal.

[8] Indeed, it is not the approach taken in, for example, Canada, France, Germany, Italy, Netherlands, Spain and Sweden

Yours sincerely

cc: