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: HB3/SLE/60847-00005/63340028
Your Ref: TA282

23 June 2017

Dear Mr McKeon

Appeal against Final Appraisal Determination - Pirfenidone for treating idiopathic pulmonary fibrosis (Review of TA282, dated June 2017)

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 June 2017). The grounds of appeal are:

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

This FAD follows an earlier Final Appraisal Determination dated September 2016, which the appellant successfully challenged on appeal.

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*".

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:

- Point of appeal 1.1(a): in determining that there was a relevant distinction between the subgroup of patients 'with a FVC between 50% and 80%' and the total population (para 4.19 FAD) the Appraisal Committee acted contrary to policy and procedures with inadequate reasons and unfairly.

- Point of appeal 1.2(a): NICE has directed itself that it is free to disregard the Appeal Panel's Decision, which is fundamentally unfair and frustrates the appellant's right of appeal.

- Point of appeal 1.3(a): the Appraisal Committee had a closed mind in respect of, and/or had predetermined, to a significant degree, the recommendation which it made.

The Appellant appeals under Ground 1(b) by reference to the detailed arguments set out in Ground 1.2(a)., which demonstrate that the Guidance Executive and/or the Appraisal Committee acted outside its powers by disregarding the Appeal Panel's Decision, thus frustrating the statutory appeal rights granted by regs 9 and 10 of the National Institute for Health and Care Excellence (Constitution and Functions) Regulations 2013/259.

The Appellant appeals under Ground 2 by reference to the detailed arguments set out in Ground 1.1(a) and Ground 1.3(a) which demonstrate that the guidance cannot reasonably be justified in the light of the evidence submitted, in that there is no rational basis for distinguishing the 50-80% subgroup from that of the total population.

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.

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 marketing 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).

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 Dr James Mawby and Ms Dawn Lee, 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 Dr Mawby and Ms Lee.
- 9 September 2016: Final Appraisal Determination issued to Roche and released publically one week later on 16 September 2016.
- 30 September 2016: Roche's appeal letter and factual error submission sent to NICE.
- 10 October 2016: NICE Vice-Chair provides an initial scrutiny letter allowing some of the grounds of appeal to proceed. Roche responds on 19 October 2016.

- 26 October 2016: NICE Vice-Chair provides the final scrutiny letter, allowing Roche's appeal to proceed on three points.
- 2 December 2016: NICE Appeal Panel meets to decide on Roche's approved appeal points.
- 20 January 2017: Appeal Panel decision is released, upholding Roche's appeal under grounds 1(a) and 2 and requiring the appraisal to be remitted to the Appraisal Committee.
- 20 April 2017: Appraisal Committee B reconsiders the appraisal in light of the Appeal Panel and Guidance Executive's directions.
- 2 June 2017: Final Appraisal Determination ("FAD") issued to Roche and released publically one week later on 9 June 2017.

As a preliminary point, the Appellant notes that the NICE Guide to the Appeals Process ("the Appeal Guide") states at para 11.2 that "*[i]f an appellant from the first appeal lodges another appeal, the appeal letter must not raise the same points presented in the first appeal or those points presented by another appellant at the first appeal hearing. The Appeal Panel will have already determined the outcome on these points.*" The Appellant understands this to mean that it is not permissible to re-argue appeal points which were unsuccessful on the first occasion, and that this does not therefore present any obstacle to any of the proposed grounds being raised in this appeal. Clearly, if an Appellant has won on an appeal point, and the Appraisal Committee repeats that exact same error again, then it would be wrong for the Appellant to be prohibited from challenging that error.

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 determining that there was a relevant distinction between the subgroup of patients 'with a FVC between 50% and 80%' and the total population (para 4.19 FAD) the Committee acted contrary to policy and procedures 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. While the possibility of subgroup analysis was raised in the Final Scope, such analysis was said to be only "*if evidence allows*".

As the Appeal Panel explained at para 28 of its Decision *"Unless a scope specifies otherwise, the Appeal Panel considers that there is a soft presumption that the starting point for any Committee should be consideration of the whole patient group as one, with a view to making one recommendation for that group. Where different recommendations are to be made for different groups of patients, the reason for departing from one recommendation should be clear and adequate. The Panel does not suggest that this should be a particularly high hurdle to surmount."*

Similarly, in para 30, the Appeal Panel said "*...the Panel tended to agree with Meindert Boysen that in a case where it appeared that use of a product was acceptably cost effective in a whole population, it would not normally be reasonable to look for subgroups within that population where use was cost ineffective.*"

In the FAD, the Committee accepted that (para 4.8 FAD) that pirfenidone is clinically effective in people with a FVC between 50% and 90% predicted and furthermore (para 4.9 FAD) that pirfenidone has the same relative clinical effectiveness in people with a FVC above 80% predicted and in people with a FVC of 80% predicted or less.

The Committee further concluded that the recommendations in NICE's previous technology approval guidance on pirfenidone "*remained appropriate for people with idiopathic pulmonary fibrosis with a FVC of between 50% and 80% predicted*" (para 4.19 FAD).

However, the Committee did not extend this recommendation to those with a FVC of between 50% and 90%. The purported basis for this distinction is set out at para 4.18 of the FAD.

This justification suffers from the same defects identified by the Appeal Panel in respect of the September 2016 FAD. In that regard, the Appeal Panel noted that it was "*not yet persuaded that it was reasonable to divide this patient population into subgroups. This is because the modelled difference in cost effectiveness between the group 50-80% and 50-90% was small, and the Committee's conclusions on the 80-90% group were tentative at best*" (para 31).

The Committee's decision does not materially advance the position. In particular, it remains the case that:

(a) The modelled difference in cost-effectiveness remains small.

   a. In respect of the total population (i.e. those with a FVC of greater than 50% predicted), the ICER (including the stopping rule) that most closely matched the Committee's preferred assumption was between £25,706 (if the Weibull distribution was used) and £28,870 (using the Gompertz distribution) per QALY assuming a 5 year treatment effect. (FAD para 4.17)

   b. In respect of the 50-80% FVC sub-group, the ICER (including the stopping rule) that most closely matched the Committee's preferred assumption was only marginally lower - between £24,933 (if the Weibull distribution was used) and £27,780 (using the Gompertz distribution) per QALY assuming a 5 year treatment effect. (FAD para 4.19).

(b) While there were uncertainties in relation to the ICERs, the Committee's conclusions in respect of these uncertainties were tentative and founded not in evidence, but in the absence of evidence (as is apparent from para 4.18 of the FAD).

(c) The third bullet point at para 4.18 of the FAD evinces an internal inconsistency in the FAD. Earlier, at para 4.14 the Committee concluded that while it did not accept the Appellant's contention that benefits lasted for at least 8 years, it was *"reasonable to assume a constant benefit up to 5*

years".[1] This is difficult to reconcile with the Committee's decision to place weight at para 4.18 on what the ICER might be if a substantially shorter (2 year) treatment effect were modelled. This internal inconsistency is in itself unfair and symptomatic of inadequate reasoning.

(d) Furthermore, as the Committee acknowledged, the ICERs in respect of the 50-80% sub-group were themselves subject to the same uncertainty relating to the stopping rule and duration of the survival benefit. In other words, they do not provide a rational or sound basis for drawing a distinction between the two groups.

Thus, the defective rationale from the first decision has been carried through into the second FAD, with no adequate reasons for the distinctions which are drawn. The inevitable consequence is that the second FAD is defective for the same reasons as the Appeal Panel found the previous FAD to be defective.

The appellant also places reliance on the remainder of its grounds of appeal as further evidence of the unfairness, and illegitimacy, of the Committee's approach to sub-groups.

In conclusion, in determining that there was a relevant distinction between the subgroup of patients 'with a FVC between 50% and 80%' and the total population (para 4.19 FAD) the Committee acted contrary to policy and procedures with inadequate reasons and unfairly.

Ground 1.2(a): NICE has directed itself that it is free to disregard the Appeal Panel's Decision, which is fundamentally unfair and frustrates the appellant's right of appeal.

As set out above, pirfenidone came back before the Appraisal Committee following a successful appeal of the previous FAD. The Appeal Panel had, in its decision upholding the appeal against that FAD, provided clear instructions as to how the further appraisal ought to be conducted.

In particular:

(a) The Appeal Panel provided guidance of general effect at para 30 of its decision in the following terms: *"in a case where it appeared that use of a product was acceptably cost effective in a whole*

---

[1] That this reflected the Committee's views was confirmed in an email from Dr Boysen of NICE dated 24 May 2017 in response to a letter from the Appellant dated 11 May 2017. In its letter of 11 May 2017, Roche raised concerns about the Committee's refusal to permit discussion or clarification of the duration of treatment effect where it had hitherto been accepted to be five years. Specifically, at the Appraisal Committee meeting, the Appellant's representatives were prohibited from making representations in relation to this matter. In his emailed response, Dr Boysen stated: "*I acknowledge there was some confusion during the meeting about the Committee's conclusion on the duration of pirfenidone's treatment effect, however I can confirm that none of the Committee's preferred assumptions have changed.*" This appears directly contrary to the earlier Report for Guidance Executive (considered in more detail in Ground 1.3(a)) in which it is said for the subgroup 50-80% that ICERs "*were at best £25-28k, using a treatment effect lasting for 5 years ..., and at worst £54K, using a treatment effect lasting for 2 years.*" The language of "at best" in inconsistent with five years being the Committee's preferred assumption (para 4.14 and 4.18 of the FAD), and fails to reflect the fact that the uncertainty pulls in both directions; the treatment effect being possibly greater than five years as well as possibly less.

population, it would not normally be reasonable to look for subgroups within that population where use was cost ineffective."

(b) The Appeal Panel then went on to provide specific guidance as to the steps which the appraisal committee "*must*" take in light of its decision at para 45: "*... the appraisal committee... must take all reasonable steps to demonstrate consideration of the effectiveness and cost-effectiveness of pirfenidone in the whole population as set out in the scope. Subgroups defined by predicted FVC could be considered if the treatment is not judged cost-effective in the whole population. The Appraisal Committee's assessment of the clinical effectiveness of pirfenidone in any subgroups should be clearly documented, including any uncertainty in the available evidence.*"

The Appeal Guide explains (at para 11.2) that where, as here, an appeal is upheld and the final draft guidance is returned to the advisory Committee, the *"The Guidance Executive will decide how to act on the decision of the Appeal Panel."* The Appellant understands that this reference means that the Guidance Executive will decide how to implement the decision of the Appeal Panel. It cannot mean that the Guidance Executive is permitted to advise the Committee to depart from a conclusion of the Appeal Panel which it disagrees with. Such an approach would be fundamentally to undermine the right of appeal granted by reg 9 of the National Institute for Health and Care Excellence (Constitution and Functions) Regulations 2013/259.

However, in this case, it appears that NICE (the Guidance Executive and/or the Appraisal Committee) directed itself that it was free to depart from the Appeal Decision. In particular:

(a) The slides used by the Appraisal Committee at the meeting on 20 April included:

a. At slide 6, entitled "*Appeal panel final conclusions*", under "*subgroups defined by predicted FVC could be considered if the treatment is not judged cost-effective in the whole population*", the comment: *"Note: economic theory (Sculpher 2008, and the Appeal panel's hypothetical considerations, support a different approach (next slide)".*

b. At slide 7, entitled "*Point 1, consideration of subgroups: statement from NICE Guidance Executive"*, the following: "NICE guidance executive *...disagree with the notion that subgroups can only be considered if the treatment is not cost effective in the whole population... [i]nstead, committee should provide a fully reasoned approach of any inclusion or exclusion of subgroup from its final recommendations."*

(b) The Appellant's concerns were put to Dr Boysen of NICE in a letter dated 11 May 2017. Dr Boysen responded in an e-mail dated 24 May 2017, in which he contended that *"where the Appeal Panel instructions do not reflect our Methods Guide, these instructions may not be supported by NICE Guidance Executive. In this case, the Guidance Executive was concerned by the Appeal Panel's suggestion that the* ***only*** *reasonable approach to considering subgroups would*

be when the whole population is not cost effective, given that economic theory (Sculpher MJ. Pharmacoeconomics 2008; 26: 799), and practice, clearly supports a different approach."[2]

(c) The "Report for Guidance Executive" dated 10 January 2017[3] (whose authors included Dr Amanda Adler, Committee B Chair and its principal spokesperson in the appeal hearing (see e.g. para 13 of the Appeal Decision)) recommended to the Guidance Executive that it "*refer the topic back to the Appraisal Committee, in line with what the Appeal Panel has suggested, but excluding the notion that "subgroups defined by predicted FVC could be considered if the treatment is not judged cost-effective in the whole population" and instead provide a fully reasoned approach of any in-, or indeed, exclusion of specific subgroups from its final recommendations*".[4]

The Appellant considers that NICE's understanding (in either or both of the Guidance Executive and the Appraisal Committee) that it is able to disregard a clear instruction from the Appeal Panel is of significant concern. Indeed, it considers this fundamentally to undermine the fairness and integrity of the assessment process. In particular, it undermines the foundational principle that assessments should be carried out with "*a very high degree of transparency in the process, with an exceptional degree of disclosure and consultation*" (*R (Eisai Ltd) v NICE* [2008] EWCA Civ 438 at para 34).

The appellant also places reliance on the remainder of its grounds of appeal as further evidence of the effect of this subversion of the process (not least in the interactions between the Committee and the Guidance Executive, behind closed doors and in the absence of the appellant).

Ground 1.3(a): the Appraisal Committee had a closed mind in respect of, and/or had predetermined to a significant degree, the recommendation which it made.

In the "Report for Guidance Executive" dated 10 January 2017 (whose authors, as noted above, included Dr Amanda Adler, Committee B Chair), the following was said about the future assessment process:

"*we expect Committee to want to make reference to the estimates of cost effectiveness that show that at best the ICERs for the ≥80% subgroup are £33-39K and at worst £80-86k, depending on assumptions*

---

[2] To the extent that "*economic theory*" is of any relevance for present purposes, and noting that Professor Sculpher is himself a member of the Diagnostics Advisory Committee and former Appraisal Committee member, (i) the abstract for that paper includes the following "*a major issue also exists concerning the appropriateness, in terms of equity, of using all or some of the subgroup analyses as a basis of decision making*"; and (ii) there are ample papers contradicting the stance taken by NICE (not least Burke et al "*Three simple rules to ensure reasonably credible subgroup analysis*" BMJ 2015; 351, and Alosh et al "*Statistical Considerations on Subgroup Analysis in Clinical* Trials" Statistics in Biopharmaceutical Research 2015; 286-303. To the extent that "practice" is of any relevance for present purposes, the Appellant understands that appraisals conducted by Committee B have recently followed precisely the approach which the Appeal Panel insisted upon – see e.g. cetuximab ID794.

[3] This was recently disclosed to the Appellant in response to a disclosure request.

[4] The Guidance Executive minutes 10.01.2017 record that the Guidance Executive agreed that the Committee should "consider the cost effectiveness of the whole population, and where it is minded to exclude a particular subgroup from its recommendations to provide a "fully reasoned approach": **Action: Meindert Boysen**." Dr Boysen's email dated 24 May 2017, set out above, and the slides for the 20 April meeting clearly show what was understood by this.

regarding duration of treatment effect (as currently referred to in the FAD). And to add that the evidence base for the ≥80% group was much smaller than that of the 50-80% group; introducing significant additional uncertainty."

In the appellant's submission, this appears to provide suggested rationales to support the recommendation made in the September 2016 FAD, namely that pirfenidone be recommended for the group 50-80%. Indeed the report as a whole (which is relied upon in its entirety) reads as though it has already been determined that the Committee will simply reach the same decision.

It is to be noted in this regard that the "Report for Guidance Executive" referred to in the previous paragraph was only shared with the Appellant in response to a specific information request from its solicitors after the Appeal Committee hearing, and indeed after the FAD had been issued. The Appellant was not provided with the opportunity to make representations in relation to this prior to the Guidance Executive reaching its decision.

Having reflected on the recently disclosed report, its tone and content reflects the appellant's experience of this second FAD process[5], which so concerned it that it wrote to Meindert Boysen in respect of them (to which Dr Boysen replied on 24 May 2017 saying "*I can reassure you that the Appraisal Committee's decision was made at the meeting on 20 April and not before*").

In the appellant's submission, the Appraisal Committee had a closed mind in respect of, and/or it had significantly predetermined the recommendation which it made.

Ground 1(b): In making the assessment that preceded the recommendation, NICE has exceeded its powers.

Ground 1.1(b): the Guidance Executive and/or the Appraisal Committee acted outside their powers by disregarding the Appeal Panel's Decision, thus frustrating the statutory appeal rights granted by regs 9 and 10 of the National Institute for Health and Care Excellence (Constitution and Functions) Regulations 2013/259

The points set out in 1.2(a) above demonstrate that the Guidance Executive and/or the Appraisal Committee acted outside their powers by disregarding the Appeal Panel's Decision. This is outside NICE's powers because it arrogates to the Guidance Executive and the Committee a right to ignore the result of an appeal. Such an approach necessarily exceeds the powers granted to NICE, as it undermines the right of appeal to an appeal panel with a majority of members who are independent of NICE; a statutory right granted by regs 9 and 10 of the National Institute for Health and Care Excellence (Constitution and Functions) Regulations 2013/259.

---

[5] For example, in preparation for the meeting on 20 April the Committee told the appellant on 24 March 2017 that if the appellant provided any further evidence then "*we would also need results for the >80% population*".

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

Ground 2.1: In determining that there was a relevant distinction between the subgroup of patients 'with a FVC between 50% and 80%' and the total population (para 4.19 FAD) the Committee drew a distinction with no rational basis.

The points set out in 1.1(a) and 1.3(a) above also demonstrate that the guidance cannot reasonably be justified in the light of the evidence submitted, in that there is no rational basis for distinguishing the 50-80% subgroup from that of the total population. In the circumstances set out above, the Committee's recommendation was unreasonable and one which no reasonable public body could have taken.[6]

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.

Yours sincerely

Sarah Ellson
Partner

cc: Kevin Jameson, Roche
Denzyl Cain, Roche

[6] It is not the approach taken in, for example, Canada, France, Germany, Italy, the Netherlands, Spain or Sweden.