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Appeals Committee Chair
National Institute for Health and Clinical Excellence
MidCity Place
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Dear

Initial Scrutiny Letter Dated 12 September 2011 ("Scrutiny Letter")

Thank you for sending us your initial views in the Scrutiny Letter. We are pleased that you have decided to allow the majority of our appeal points. However, we would be grateful if you could review your initial position with respect to a number of our arguments relating to: the use of dasatinib as combination therapy; the patient access scheme; the End-of-Life criteria; and the ultra-orphan points. We set out our reasons below.

Ground 1.2: The Institute's Choice of Comparator is Inconsistent with the Methods Guide.

We confirm that we shall be arguing that the inconsistency has caused procedural unfairness.

Ground 1.3: Considering Dasatinib as Combination Therapy in the Blast Phase of CML is Unfair.

The Scrutiny letter states that there is no evidence from the FAD that the Appraisal Committee had considered dasatinib as combination therapy. This is untrue; during the appraisal process, NICE clearly discussed with clinical experts the role of dasatinib as combination therapy in the blast phase. This is also made apparent in paragraphs 4.3.27 to 4.3.29 of the FAD.

BMS feels that these considerations influenced the Appraisal Committee's decision not to recommend dasatinib in the blast-phase of treatment, something we argue is unfair. This is particularly relevant when, as a consequence, patients are left with no other meaningful treatment option other than a bone marrow stem cell transplant – a procedure which is not a realistic option for a large proportion of patients. We request that you refer this matter to the appeal panel for consideration.

Ground 1.4: The Review and Approval of Novartis' Patient Access Scheme During an On-Going Multiple Technology Appraisal Is Procedurally Unfair.

The Scrutiny Letter suggests that NICE is somehow detached from the PPRS patient access scheme approval process and, in any event, adds that NICE must seek to incorporate an approved scheme

into an appraisal where possible. We respectfully disagree with these views. For the reasons below and those set out in our appeal letter, NICE is very much involved in reviewing patient access schemes as part of the PPRS process and deciding if and when they should be incorporated into an appraisal.

The PPRS is an arrangement between the UK Health Departments and the ABPI that provides greater flexibility over pricing of products through various means, including patient access schemes.

Section 6 of the PPRS provides the principles and operational context of patient access schemes in the NICE appraisal process. Patient access schemes must be agreed in principle first with the Department of Health, which reviews the proposal primarily to ensure that the scheme would not place an administrative burden on the NHS. NICE's patient access scheme liaison unit (PASLU) is intimately involved in this aspect of the review to ensure that the scheme is "feasible".

However, the acceptance of patient access schemes into the NICE appraisal process is ultimately a decision for NICE. For the reasons set out in our appeal letter, and explored further below, the strong presumption is that schemes will not be accepted into a multiple technology appraisal process during an existing appraisal. This is to avoid *"gaming"* by *"any party"*, which we consider includes not only pharmaceutical companies and the Department of Health, but also NICE (Paragraph 6.33 of the PPRS). Schemes must therefore only be submitted at the beginning of a multiple technology appraisal, or after final NICE guidance has been issued.

Paragraph 6.26 of the PPRS summarises the key principles of patient access schemes and the roles of various parties. With respect to NICE, it states:

> *"NICE's principal role is to assess the impact of such proposals on cost-effectiveness taking into account the details of the proposed scheme."*

NICE therefore plays a key part in the patient access scheme process and is ultimately responsible for accepting a proposed scheme into a NICE technology appraisal. As we mentioned in our appeal letter, the PPRS sets out specific timing provisions in the context of a multiple technology appraisal such as this. Paragraph 6.36 of the PPRS states:

> *"If the company wishes to propose a patient access scheme they should submit proposals to NICE (post discussions with the Department) at the start of the MTA process. Because of the complexity of the MTA process, there must be a very clear presumption against proposing or accepting schemes at additional times in the NICE process."*

The PPRS also adds a provision in paragraph 6.44 regarding patient access scheme consultations, which makes clear the need to consult about such schemes. It states:

> *"When NICE consults on draft appraisal guidance, this must provide stakeholders with an opportunity to comment on the full content of the appraisal including the details of any proposed pricing scheme."*

NICE is therefore inextricably linked to the PPRS itself, as made clear by the provisions above, as well as the Department of Health's statement in the PPRS that the *"scope of influence is limited to the NHS in England and NICE"* (Paragraph 6.4). Regardless of the clear language in the PPRS

itself, NICE is a special health authority that is part of the NHS and must, therefore, take account of the PPRS when considering the timing of patient access scheme submissions into an appraisal. Indeed, NICE's own guidance on the multiple technology appraisal process states that patient access schemes will only be accepted after an ACD **in exceptional circumstances** (emphasis added). In such exceptional circumstances, the guidance states that an ACD will be re-issued unless the guidance *"remains positive or largely positive"*. If the guidance remains positive, then the guidance states that NICE will issue a FAD (Paragraph 5.9 of the Multiple Technology Appraisal Process Guide (2009)).

Your scrutiny letter states that you are "unclear" as to why this has caused unfairness to BMS specifically. Your letter states: "*It appears to me you could have submitted a patient access scheme of your own had you wished to do so.*" With the above points in mind, we consider that the acceptance by NICE of a patient access scheme outside the clear timing provisions for multiple technology appraisals under the PPRS is unfair. If such a scheme is accepted, then we would wish to be consulted on the reasons for accepting the scheme mid-way through an appraisal. We would also wish to comment on the scheme itself, subject to any commercially sensitive information being redacted.

In this case, we are unaware of any exceptional circumstances that would justify the acceptance of a scheme after an ACD. Further, we consider that the current recommendations in the FAD, which incorporates Novartis' scheme are still largely negative (i.e. the recommendations have not remained *"positive or largely positive"*). This is because although nilotinib has been recommended, the scope of the recommendation applies only to patients with the chronic and accelerated forms of the disease. Both dasatinib and high-dose imatinib have not been recommended, leaving patients with limited treatment options and no meaningful treatment option for the blast phase of the disease.

Therefore, NICE should have re-issued the ACD in accordance with its process guide, or proceeded to issue a FAD without incorporating the scheme. In the latter scenario, any consideration of patient access schemes would take place after final guidance has been issued. At this point, after the procedure had run its normal course, BMS (and others) would have been able to submit a patient access scheme. However, by forging ahead with issuing a FAD, NICE has presented BMS and others with a *fait accompli*.

If NICE was minded on changing its process on patient access schemes, it should have let all consultees know at the same time and provided a window of opportunity for BMS to submit its own scheme mid-way through an appraisal. The failure to notify BMS, and the other consultees, that a patient access scheme had been submitted - particularly when NICE accepted the scheme outside the clear timelines set out in the PPRS - discriminates against the company and dasatinib.

Finally, we consider that the acceptance of the scheme by NICE immediately prior to issuing the FAD further compounds the overall unfairness of this appraisal process. It suggests that NICE simply issued its recommendations without following due process (e.g. with respect to the imatinib-intolerant population, or addressing our concerns over the modelling used in this appraisal (e.g. any PAS incorporated into the appraisal based on the Assessment Group's modelling must surely be perverse given the inherent flaws in the model). We feel strongly, therefore, that this point should be put before the appeal panel, who may wish to consider the overall fairness of the appraisal.

Ground 1.5: The Decision Not to Apply The End-of-Life Criteria is Unfair.

The Scrutiny Letter suggests that NICE's End-of-Life Guidance is clearly worded such that the Appraisal Committee was justified in not applying the guidance. We respectfully disagree with this view. We have inserted the relevant section - Section 2 - from the End-of-Life Guidance in full below. This makes absolutely clear that when the conditions in paragraph 2.1 are met then the Appraisal Committee **must** consider the factors in paragraph 2.2. If there is any discretion, then this appears to be in the wording of paragraph 2.3., which suggests that the Appraisal Committee *"will need to be satisfied"* that, among other things, the data are robust and the modelling are *"plausible and objective"*.

> **"2 Criteria for appraisal of end of life treatments**
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> 2.1 This supplementary advice should be applied in the following circumstances and when all the criteria referred to below are satisfied:
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> > 2.1.1 The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
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> > 2.1.2 There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment, and;
> >
> > 2.1.3 The treatment is licensed or otherwise indicated, for small patient populations.
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> 2.2 When the conditions described in 2.1 are met, the Appraisal Committee will consider:
>
> > 2.2.1 The impact of giving greater weight to QALYs achieved in the later stages of terminal diseases, using the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy individual of the same age, and;
> >
> > 2.2.2 The magnitude of the additional weight that would need to be assigned to the QALY benefits in this patient group for the cost-effectiveness of the technology to fall within the current threshold range.
>
> 2.3 In addition, the Appraisal Committees will need to be satisfied that:
>
> > 2.3.1 The estimates of the extension to life are robust and can be shown or reasonably inferred from either progression free survival or overall survival (taking account of trials in which cross-over has occurred and been accounted for in the effectiveness review). and;
> >
> > 2.3.2 The assumptions used in the reference case economic modelling are plausible objective and robust."

However, the Appraisal Committee did not give any consideration to the factors in paragraph 2.2, merely dismissing an analysis of dasatinib under the End-of-Life Guidance. This is unfair.

BMS considers that this point should be heard under Ground 1 and Ground 2 at an oral hearing, particularly given that we are dealing with a life-extending treatment. In such circumstances, case law on human rights makes clear that the decision requires particular, detailed, scrutiny.[1]

Our procedural argument under this ground is inextricably linked to our argument under Ground 2 – that the Appraisal Committee acted unreasonably in suggesting that the data are not robust. This is because the definition of robust in the end-of-life setting should surely be different to that routinely applied in health technology assessments (i.e. data obtained via comparative randomised, controlled trials [RCTs]). By definition, the population to which end-of-life applies in CML (i.e. patients in blast crisis who have failed imatinib therapy) consists of such a small number of patients that such RCT data generation would extremely difficult, if not impossible. It should be emphasised that the available data demonstrate a period of overall survival in excess of that which would be expected for this group of patients.

Ground 2.1: Relying on outputs of the SHTAC Model and utilising these to form the basis of guidance to the NHS is Perverse.

We shall provide you with supplemental arguments under this ground by 3 October 2011 as requested.

Ground 2.5: Ultra-Orphan.

The Scrutiny Letter states that you are not presently minded to refer our ultra-orphan argument to the Appeal Panel. You refer to two documents we cited in support of this argument, namely the Social Values Judgment publication and draft guidance on the Institute's website on assessing orphan and ultra-orphan drugs.

Regarding the Social Value Judgement document, you state "*It is correct that the document states that NICE does not expect to be asked to evaluate "ultra orphan" drugs, but I do not understand how that expectation supports the proposition that, if such drugs are referred, they must be approached differently.*" You add that the draft guidance issued by NICE on appraising orphan and ultra-orphan drugs was considered in the following appeal: "Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia" and conclude that "*I cannot see on what basis an appeal panel would depart from those views*".

The main thrust of our ultra-orphan argument under Ground 2 is that the Institute (and through it the Appraisal Committee) has acted unreasonably in applying the same assessment criteria to dasatinib as it would for an orphan or non-orphan medicine. This is because the ICERs generated for ultra-orphan drugs are almost always outside the cost-effectiveness thresholds acceptable to NICE, as evidenced by the draft guidance on the Institute's website. The draft guidance clearly states that ultra-orphan drugs are likely to be *"cost ineffective"* as a matter of default. The date of the draft guidance, and whether or not it is marked *"final" or "draft"*, is irrelevant. It is clearly known to the Appraisal Committee.

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[1] *R (Rogers) v Swindon NHS Primary Care Trust* [2006] 1 WLR 2649, § 56 "*... the case is concerned with a decision which may be a life or death decision for the claimant. In these circumstances .... it is appropriate for the court to subject the decision to refuse funding for the treatment (and thus in practice the treatment) to rigorous scrutiny.*"

We are not arguing that NICE is bound to follow a different procedure as a matter of process (something we would have argued under Ground 1). Rather, we are arguing that it is unreasonable for the Institute to apply the same criteria to dasatinib as for non-ultra-orphan medicines.

Whether it was reasonable or not is something that we consider should be heard at an oral hearing, particularly as we are dealing with a life-extending treatment. In such circumstances, particular scrutiny of the decision is required.

The appeal panel decision in the azacitidine case does not affect this analysis. Indeed, in the azacitidine case, we note that the Appraisal Committee considered azacitidine in the context of NICE's End-of-Life guidance, something that the Appraisal Committee has failed to do in dasatinib's case.

Ground 3.1: The FAD Recommendations are in Breach of the Human Rights Act 1998.

We shall provide you with supplemental arguments under this ground by 3 October 2011 as requested.

Ground 3.2: The Acceptance of the Novartis Patient Access Scheme is in Breach of the PPRS.

The Scrutiny Letter suggests that compliance with the PPRS is a matter for the Department of Health. For the reasons set out above (Ground 1.4), the acceptance of the scheme as part of an existing multiple technology appraisal process is a decision for NICE. The scope of NICE's powers to accept such an scheme is set out in the PPRS, which was negotiated by the Department of Health taking into account its influence over NICE as a special health authority, and NICE guidance on the multiple technology appraisal process.

Next steps.

We hope that you accept our additional points above regarding Grounds 1.3, 1.4, 1.5, 2.5 and 3.2 and refer these issues to the appeal panel for consideration. We look forward to hearing from you and remain on hand to answer any questions you may have.

We would also like to take this opportunity to request that a stenographer be present during the appeal to transcribe the hearing. We would be happy to meet the cost of this service and share the transcript with the Appeal Panel and other Appellants.

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Yours sincerely

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