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September 2nd, 2011

Chair, Appeal Committee
National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
London
WC1V 6NA

Dear !

Appeal Against Final Appraisal Determination: Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) (part review of NICE technology appraisal guidance 70), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance

Following NICE's letter to Bristol-Myers Squibb, dated 11 August 2011, enclosing the Final Appraisal Determination (FAD) for the above technology appraisal.

We hereby confirm that in accordance with the procedures set out in the letter and the "Guidance for appellants", Bristol Myers Squibb wishes to appeal 8 aspects of the appraisal and the resultant proposed guidance on 3 grounds of appeal, as set out below in more detail:

- The splitting and subsequent combining of the appraisals of dasatinib and nilotinib for CML was undertaken without adequate consultation, transparency and procedures and therefore unfairly deprived consultees of their procedural and administrative rights.

- In addition, a number of unfair, perverse and ultra vires outcomes, are noted:

- the selection of hydroxycarbamide to represent routine care or best practice. Hydroxycarbamide is an antiquated therapy in this setting and FAD recommendations based on this comparator fail to follow the Institute's own guidance on the selection of relevant comparators, and fail to take into account consistent input from stakeholders asserting that the comparator is non-relevant;

- inadequate consideration of the imatinib-intolerant population and failure to consult adequately with stakeholders to ensure appropriate consideration of this population;

- an arbitrary reliance on an economic model that is not fit for purpose and a consequent reliance on the "least implausible" ICER;

- an attempt to introduce an appraisal of dasatinib in combination with acute leukaemia-style chemotherapy for patients in blast phase;

- acceptance of a patient access scheme during the course of a Multiple Technology Appraisal, in breach of the Pharmaceutical Price Regulation Scheme 2009 and resulting in unequal and discriminatory treatment against Bristol-Myers Squibb (BMS);

- an unfair and perverse interpretation of NICE's supplementary guidance on end-of-life therapies;

- a lack of transparency by failing to provide BMS with a fully executable version of the Assessment Group's models; and

- issuing recommendations that will unreasonably deprive CML patients, in the blast phase of their disease, of any meaningful treatment, in breach of their human rights.

We therefore ask that the Appeal Panel request a re-appraisal based on a de novo model or request the Decision Support Unit reconsider the evidence presented as well as taking into account all the available longer term evidence generated to date.

Alternatively, bearing in mind that the Appraisal Committee considered the "least implausible" ICER for dasatinib to be £43,816 per QALY gained, we urge the Appeal Panel to direct the Appraisal Committee to exercise its discretion in recommending dasatinib, notwithstanding that in comparison to the correct comparator (imatinib), dasatinib is either likely to be considered cost effective at conventional levels or dominant (it is less costly and more effective).

1. The Institute has failed to act fairly

1.1 The splitting and subsequent combining of the appraisals of dasatinib and nilotinib for CML lacks transparency and has deprived consultees of their procedural and administrative rights.

NICE announced on 9 February 2010 that it had agreed with the Appraisal Committee (without formal consultation with stakeholders) to split the appraisal of dasatinib and nilotinib for chronic myeloid leukaemia into two separate appraisals.[1] The press release stated:

> "To effectively appraise a new treatment, the Committee compares it to an existing one. In this case, high dose imatinib (glivec, 600 mg or 800 mg per day) has been identified as a comparator for dasatinib and nilotinib for people who are 'resistant' to imatinib (standard treatment with imatinib (400 mg per day) has stopped working), although it clearly cannot be a comparator for people who cannot tolerate imatinib.
>
> NICE is about to start a review of its current guidance on high dose imatinib for chronic myeloid leukaemia (TA70), **so this review will now incorporate an appraisal of dasatinib and nilotinib compared with high dose imatinib for people who are 'resistant' to standard imatinib treatment. The current appraisal will continue for 'imatinib intolerant' people only.**" (Emphasis added.)

[1] See NICE press release of 9 February 2010, available at: http://www.nice.org.uk/media/AD8/84/2010012DasatinibAndNilotinibForCMLACD2.pdf, last accessed 15 August 2011.

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In addition, BMS were notified of the changes and felt reasonably assured at the time of the announcement that the correct comparator had been identified by NICE for imatinib-resistant patients. However, when the draft scope for the imatinib-resistant appraisal was published, we and others were surprised and deeply concerned that high-dose imatinib was not included as the comparator.

Rather, it appears that NICE and the Appraisal Committee proposed, without public consultation, to include high-dose imatinib as a technology for appraisal rather than a relevant comparator. The draft scope also referred to a number of obsolete and antiquated drugs for CML as comparators. BMS and other consultees made clear in responding to the scope that:

> "These treatments are not currently used in the NHS for adults with chronic myeloid leukaemia in the chronic, accelerated or blast phase who are resistant to low-dose imatinib. High dose imatinib (600mg or 800mg) should be the only comparator as it is accepted as standard of care. Chemotherapy with hydroxycarbamide or busulfan and IFN are not used in current practice and cannot be considered as 'best alternative care'."[2]

Despite this dialogue, high dose imatinib was excluded as a comparator in the final scope for imatinib resistant patients.

Further, we were informed by NICE without consultation that, following the Appraisal Committee discussion held on the 9 June 2011, they intended to release one FAD combining the recommendations not only for people with imatinib-resistant CML but also for those with imatinib-intolerant CML.

BMS has serious concerns about the procedures that NICE followed regarding their decision to split and re-combine the appraisals. There is no guidance in NICE's Guide to the Methods of Technology Appraisals[3] (Methods Guide) on these issues, but BMS has a legitimate expectation that it and other consultees would be consulted,[4] and the lack of consultation and transparency on these points is unfair, particularly when considering the following:

- The decision to split the appraisal process in 2010 presupposed that high-dose imatinib was the most appropriate comparator for the imatinib-resistant population. The lack of a formal consultation process on the decision to split the appraisal has meant that high-dose imatinib has become a technology under appraisal rather than a comparator. This has led to a number of perverse outcomes, in particular the selection by the Appraisal Committee of a comparator (hydroxycarbamide) that is not used for imatinib resistant patients in clinical practice (see Ground 2 below).

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[2] See Consultation comments on the draft scope for appraisal of dasatinib, high dose imatinib and nilotinib for the treatment of chronic myeloid leukaemia (part review of Technology Appraisal No. 70), available at: http://www.nice.org.uk/nicemedia/live/13003/49805/49805.pdf, last accessed 15 August 2011.

[3] Guide to the Methods of Technology Appraisal, National Institute for Health and Clinical Excellence, June 2008 (N1618). See http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf, last accessed 30 August 2011.

[4] The law in this area was recently and helpfully summarised in *R (on the application of Luton Borough Council and others) v Secretary of State for Education)* [2011] EWHC 217 (Admin), which provides that persons with a legitimate expectation of consultation must be consulted before "taking any step or decision".

- The subsequent re-combination of the appraisal for imatinib-intolerant patients has not been conducted in an open and transparent manner. BMS and others had submitted comments on the Appraisal Consultation Document (ACD) prior to the split and subsequently on the ACD published for imatinib-intolerant patients after the split. However, the FAD contains no reference to these ACD's, and merely states that estimates of cost-effectiveness could be "inferred"[5] from cost-effectiveness estimates for the imatinib-resistant population, even though the Southampton Health Technology Appraisal Centre (SHTAC) report "did not address imatinib intolerance"[6]. The failure to provide meaningful information about the imatinib-intolerant population in this FAD and/or adequate reasons relating to NICE's rejection of dasatinib for imatinib-intolerant patients is contrary to the principles of natural justice and unfairly prejudices BMS, particularly when considering the likely weight given to Novartis' Patient Access Scheme (see section 1.4). Indeed, NICE's press release on the FAD suggests that on receiving the Patient Access Scheme, NICE simply went ahead with issuing recommendations without considering fully the issues raised by consultees.[7]

1.2 The Institute' choice of comparator is inconsistent with the Methods Guide

The Appraisal Committee considered that the most appropriate modelled analysis was the SHTAC scenario in which the key comparator was hydroxycarbamide. However, hydroxycarbamide is not used routinely in the NHS in this setting, nor does it constitute best practice (see also Ground 2). The choice of comparator is therefore unfair and inconsistent with the Methods Guide, which states:

> *"Relevant comparators are identified, with consideration given specifically to* ***routine*** *and* ***best practice*** *in the NHS (including existing NICE guidance) and to the natural history of the condition without suitable treatment.* ***There will often be more than one relevant comparator technology because routine practice may vary across the NHS and because best alternative care may differ from routine NHS practice.*** *For example, this may occur when new technologies are used inconsistently across the NHS."* (emphasis added.)[8]

1.3 Considering Dasatinib as Combination Therapy in the Blast Phase of CML is unfair

The FAD states at paragraphs 4.3.27 to 4.3.29 that patients in the blast phase of CML are treated generally using dasatinib in combination with intensive chemotherapy for acute leukaemia. The FAD adds that no data were presented to support this treatment scenario.

This appraisal is to assess dasatinib and other technologies as monotherapies in accordance with the final scope. An appraisal of the clinical and cost-effectiveness of dasatinib in combination with intensive chemotherapy for acute leukaemia in blast phase CML would constitute a new appraisal

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[5] See paragraph 4.3.20 of the FAD.

[6] See paragraph 4.1.2. of the FAD

[7] See NICE press release on the FAD, available at: http://www.nice.org.uk/newsroom/pressreleases/DasatinibImatinibAndNilotinibForIRIICMLFAD.jsp, last accessed 30 August 2011. The press release states: "*However, during consultation on draft recommendations, the manufacturer of nilotinib agreed to provide the drug to the NHS at a discounted price. This reduction in cost enabled the independent Committee to approve nilotinib for use on the NHS.*"

[8] See paragraph 2.2.4 of the Methods Guide

that must be subject to the usual procedural processes and safeguards, including a scoping exercise, consultation with parties and the opportunity for BMS to make detailed submissions. In such circumstances, BMS would have pointed out that the treatment of CML in the blast phase described in the FAD is not representative of the significant proportion of patients presenting in the blast phase who cannot undergo acute leukaemia-style chemotherapy treatment due to age-related comorbidities.

Once patients progress to blast crisis, the only option likely to achieve long-term good health is a bone marrow stem cell transplant (BMSCT). However, even though this procedure is the only option likely to give these patients any long-term benefit, very few patients at this stage of their disease will be eligible (or fit enough) for BMSCT. This is because non-white Caucasians are frequently unable to achieve a suitable transplant donor match, as well as the fact that a typical BMSCT recipient is under 45 years of age, with few (if any) significant co-morbidities. This means that, as stated in the BMS submission (the evidence for which was gathered by taking a consensus poll of senior BMSCT physicians), transplantation really is a realistic treatment option for only a restricted number of CML patients in blast crisis (at most approximately 30%).

This position is supported by the Royal College of Physician's ACD response, which states:

> "Only dasatinib has a product licence for blast crisis, but clinical experience suggests that it may palliate the unpleasant symptoms of blast crisis for many months, ensuring reasonable quality of life for the majority of patients. This is especially important for the considerable number of patients who cannot undergo acute leukaemia-style treatment. It appears that blast crisis may therefore meet NICE criteria for 'end of life', and indeed this point was made at the April appraisal committee meeting."

We also make similar arguments under Ground 2 (End-of-Life) below.

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

Section 1.1 of the FAD recommends nilotinib, provided that Novartis makes it available with the discount agreed as part of the Patient Access Scheme. We are surprised by NICE's acceptance and consideration of Novartis' Patient Access Scheme in a manner that is clearly outside the terms of the Pharmaceutical Price Regulation Scheme 2009 (PPRS). The timing of the submission and acceptance of Patient Access Schemes was recognised as a crucial aspect of the PPRS and detailed provisions on timing were agreed and included to ensure that such schemes do "not encourage 'gaming' of the appraisal system by any party."[9]

Paragraphs 6.34 to 6.35 of the PPRS deal with the timing of Patient Access Scheme proposals in the context of a Single Technology Appraisal, which envisages that schemes may be submitted during the course of an on-going appraisal, although this would be the exception rather than the norm.

Paragraphs 6.36 to 6.39 of the PPRS provide the basis for PAS submissions in the context of Multiple Technology Appraisals (MTAs). Paragraph 6.36 states:

[9] See paragraph 6.33 of the PPRS, available at: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_098498.pdf, last accessed 15 August 2011.

> "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.**" (emphasis added)

Paragraph 6.38 of the PPRS recognises that in the event of a negative recommendation in final guidance issued by NICE in an MTA, a company may submit a Patient Access Scheme for rapid view, as is the case in the Single Technology Appraisal process.

Unfortunately, NICE's process guide to the Multiple Technology Appraisal process (2009),[10] as amended following the PPRS, misinterprets the PPRS provisions relating to timing of Patient Access Scheme submissions. The NICE guidance suggests that patient access schemes can be submitted at any time during an on-going MTA appraisal. However, according to the PPRS, this is only the case for single technology appraisals. Indeed, when NICE consulted on the amendments to its process guides to factor in Patient Access Schemes, it admitted:

> "A new section five of both guides has been included to cover the requirements of the 2009 PPRS agreement, and is now open for consultation (see links below). **The version we are consulting on is tailored specifically for the STA Process Guide. The MTA version is the same in content with just the relevant references altered.**"[11] (emphasis added).

It is clear, therefore, that NICE did not appreciate the timing issues over Patient Access Schemes in the MTA context and relied solely and inappropriately on the provisions on timing in the STA context.

To conclude, NICE has accepted a scheme outside the provisions of the PPRS without giving any reasons for the clear presumption against accepting such submissions. Accepting a scheme in these circumstances without affording BMS an opportunity to submit its own patient access scheme at the same time as Novartis, or imposing some procedural rigour on such a submission is: in breach of the PPRS; conflicts with the principle of natural justice; results in unequal treatment; and unfairly prejudices dasatinib and BMS (see also Ground 3).[12]

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

The Appraisal Committee states at paragraph 4.3.29 of the FAD that the end-of-life criteria defined by NICE in its supplementary advice does not apply to dasatinib for people with blast-crisis phase CML on the basis that the available evidence was "too weak and was not considered to be robust. In addition, no data were presented for the interventions as used in clinical practice."

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[10] Guide to the multiple technology appraisal process, NICE, October 2009 (N2022) at section 5. See http://www.nice.org.uk/media/42D/8C/MTAGuideLRFINAL.pdf, last accessed 15 August 2011.

[11] Review of the single and multiple technology appraisal processes, available at http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/reviewofthesingleandmultipletechnologyappraisalprocesses.jsp, last accessed 15 August 2011.

[12] See paragraph 5.1 of the process guide: http://www.nice.org.uk/media/42D/8C/MTAGuideLRFINAL.pdf, last accessed 15 August 2011.

However, the NICE guidance for "Appraising life-extending, end-of-life treatments" (End-of-Life Guidance)[13] states that the End-of-Life Guidance "will" apply if all the criteria in paragraph 2.1 are met. These are:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment
- The treatment is licensed or otherwise indicated for small patient populations.

Patients who present with blast-stage CML typically have 3-6 months to live and patients with blast phase CML treated with dasatinib have demonstrated a median overall survival of 8-11 months.[14] The FAD records that approximately 560 people are diagnosed with CML in the UK each year,[15] and fewer of these will present in the blast phase. Dasatinib therefore meets the criteria in the End-of-Life Guidance and the Appraisal Committee must go on to consider the following elements described in paragraphs 2.2 of the guidance:

> "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." (Emphasis added.)

However, the Appraisal Committee did not give any consideration to these factors and merely dismissed an analysis of dasatinib under the End-of-Life Guidance by relying solely on paragraph 2.3 of the End-of-Life Guidance, which lists further considerations for the Appraisal Committee when exercising its discretion, i.e., that the data 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*
>
> *The assumptions used in the reference case economic modelling are plausible objective and robust."*[16]

The failure to follow the End-of-Life Guidance is procedurally unfair. The conclusion that the data are not robust is perverse (see Ground 2 below).

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[13] Appraising life-extending, end of life treatments, NICE, Revised July 2009. See http://www.nice.org.uk/media/E4A/79/SupplementaryAdviceTACEoL.pdf, last accessed 15 August 2011.

[14] See Dasatinib's Summary of Product Characteristics available at: http://www.medicines.org.uk/emc

[15] Paragraph 2.4 of the FAD.

[16] See paragraph 2.3 of the End-of-Life Guidance.

1.6 The failure to provide BMS with a fully executable version of PenTAG/SHTAC model lacks transparency

BMS has been deprived of the opportunity to provide fully informed comments on the modelling used by PenTAG and SHTAC because the probabilistic sensitivity analysis was both incorrectly constructed and could not be run. Had BMS been able to check, comment and run the probabilistic sensitivity analysis, we believe that we would have been able to generate a 95% confidence interval for our ICERs, which would provide greater certainty for the Appraisal Committee.

As NICE is aware, the model used by the Assessment Group is central to the Appraisal Committee's determination of a drug's cost-effectiveness and in particular to the cost per QALY and whether it comes within the threshold of acceptable cost. Paragraph 5 of NICE Methods Guide states:

> "*The estimates of clinical and cost effectiveness are, individually, key inputs into the decision-making of the Appraisal Committee. It should also be emphasised that they are interdependent because comprehensive, transparent and reproducible synthesis of all relevant evidence on health effects is needed for high-quality, cost-effectiveness analysis.*".

The robustness or reliability of the model is therefore a key question. For the thorough testing of reliability, there can be no doubt that a fully executable version is required, especially if a manufacturer wants to carry out a sensitivity analysis. Without a fully executable version, the company is limited in what it can do to check and comment on the reliability of the model itself because the company only received a read-only version. The failure to provide BMS with such a model is unfair and has left BMS "*making shots in the dark, in circumstances where the light could so easily be switched on*".[17]

2. The Institute has formulated guidance that cannot reasonably be justified in the light of the evidence submitted

The FAD contains a number of mistakes of fact and misinterpretations of the clinical and cost-effectiveness evidence for dasatinib. These errors have led to the perverse decision to rely on hydroxycarbamide as the key comparator and a perverse reliance on the "least implausible" model as the basis for recommendations to the NHS. Further, the Appraisal Committee has unreasonably concluded that the data available for dasatinib in the blast phase of CML are not robust enough to apply its end-of-life criteria, despite such data forming the basis of the marketing authorisation for dasatinib as approved by the European Commission.

The decision by the Appraisal Committee therefore clearly does not add up, which is the appropriate standard of unreasonableness.[18]

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[17] *R (on the application of Eisai Ltd) v National Institute for Health and Clinical Excellence* [2008] EWCA Civ 438, at paragraph 50.

[18] *R v Parliamentary Commissioner for Administration ex p. Balchin* [1998] 1 PLR 1: "The applicant does not have to demonstrate, as respondents sometimes suggest is the case, a decision so bizarre that its author must be regarded as temporarily unhinged. What the not very apposite term 'irrationality' generally means in this branch of the law is a decision which does not add up - in which, in other words, there is a error of reasoning which robs the decision of logic."

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

The Appraisal Committee states that none of the economic models had presented a plausible ICER,[19] yet it has chosen to rely on the "least implausible" analysis of the SHTAC scenario in which a number of the assumptions are completely unreasonable, do not reflect clinical practice and focus on an obsolete comparator – hydroxycarbamide.

In these respects, the economic model is not fit for purpose according to good practice in economic modelling and the Institute's Methods Guide.

- 3.1.3 states that 'the analyses and modelling should be methodologically sound'
- 3.1.4 states that 'Economic models should also: have face validity (that is, be plausible)
- 6.2.18 states that 'The Committee's judgements on cost effectiveness are influenced by the following factors: the robustness and appropriateness of the structure of the economic models

In multiple respects, the SHTAC model fails to meet the standards set by the Institute and we re-present key points of weakness in the model in Appendix 1. BMS along with other stakeholders to the appraisal have consistently raised these points for consideration.

No effort was made to change this flawed modelling approach and, as noted by the Appraisal Committee, the SHTAC's revised version did not fix this fundamental problem, but merely altered some data outputs. In addition, the SHTAC analysis makes no effort to model the underlying disease and, by the admission of the Appraisal Committee, is only a minor modification of the (flawed) PenTAG model.

The arbitrary nature in which the Appraisal Committee has selected a flawed model is perverse. This is compounded by the availability of models submitted during the appraisal which meet a higher standard in terms of good practice in economic modelling. The original PenTAG Assessment Report[20] provides a review of the economic models submitted by manufacturers according to the NICE Reference Case and according to a critical appraisal checklist; the latter authored by experienced health economists and published in a respectable peer-review journal.

Assessed against these criteria the models submitted were consistently evaluated to be structured appropriately to model the disease process and to be methodologically sound. Where the models are criticised is in terms of the data inputs selected. However, in this regard alone the models therefore meet a higher standard of suitability for a NICE assessment than the PenTAG / SHTAC model with its inherent inability to accurately model the disease process. Against this background, the Appraisal Committee's choice of model clearly does not add up and is perverse.

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[19] Paragraph 4.3.19 of the FAD.

[20] Dasatinib and nilotinib for imatinib-resistant or –intolerant chronic myeloid leukaemia: A systematic review and economic evaluation. NIHR HTA Programme project number 08/31/01 at Appendix 4, available at http://www.nice.org.uk/nicemedia/live/12029/46136/46136.pdf, last accessed 31 August, 2011.

2.2 The choice of hydroxycarbamide as the most appropriate comparator is perverse

In place of high-dose imatinib as the key comparator, the Appraisal Committee has chosen to shift its focus to the use of hydroxycarbamide, despite it representing antiquated clinical practice in this setting, as made clear by clinical expert submissions during the course of this appraisal. The Appraisal Committee has clearly ignored the clinical expert opinion, as well as BMS and other consultees, on this point. Furthermore, despite agreeing that any one of a range of treatments could be considered as a comparator, the Appraisal Committee has arbitrarily decided to focus solely on hydroxycarbamide, justifying this on the basis that the analyses presented by SHTAC were the "least implausible", without justification and without reference to other relevant comparators.

For instance, in response to the suggestion in the Appraisal Consultation Document (ACD) that clinical specialists told the Appraisal Committee that, in the absence of dasatinib, high-dose imatinib or nilotinib, hydroxycarbamide or stem cell transplantation would be used, Dr. Jane Apperley, representing the Royal College of Physicians (RCP) and other professional bodies, commented:

> "The clinical specialists stated on many occasions that if a patient was resistant to imatinib but remained in chronic phase that the most likely scenario would be that they remained in imatinib 400mg or where possible were given an increased dose."

In ignoring the clinical advice, the Appraisal Committee has shifted its review from an area where there is a significant body of evidence to an area for which there is, inevitably, almost no evidence and where evidence is unlikely ever to arise.

Any attempt to set up clinical trials in order to generate data comparing dasatinib or nilotinib to hydroxycarbamide would be unethical. This is because the Declaration of Helsinki requires that clinical research involving any "new intervention" must be conducted against the "best current proven intervention" and that the use of other interventions, placebo or no therapy is only possible if "no current proven intervention exists". The 1996 version of the Declaration, which applies to all pharmaceutical clinical research within the European Union, provides:

> "[i]n any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists."

In fact, in their response to the ACD, the RCP states that "several clinical study groups including the NCRI Haematological Oncology (CML subgroup) Clinical Studies Group have felt it impossible to design a Randomised Controlled Trial (RCT) of the appraisal technologies against standard dose imatinib, in a population of patients in whom the latter has already failed".

These issues are particularly relevant in the oncology field. By selecting hydroxycarbamide as the most appropriate comparator, the Appraisal Committee is moving from a position where it has meaningful data to a position that is likely to remain evidence free.

It is therefore perverse of NICE to make a reimbursement decision for a whole class of interventions based on a flawed economic model and equally perverse to accept a Patient Access Scheme predicated on such modelling.

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2.3 The Decision Not to Apply The End-of-Life Criteria to Blast Crisis Patients is Perverse

As mentioned in paragraph 1.5 above, BMS considers that the failure to apply the End-of-Life Guidance is procedurally unfair. The conclusion that the data are not robust is perverse, especially when a major robustness criticism of the data surrounds the lack of information on concealment allocation identified by the Assessment Groups in their analysis. This is despite the fact that BMS subsequently provided this data to the Appraisal Committee.

Even in the absence of comparative data for accelerated and blast phase disease, it is difficult to understand why the Appraisal Committee considers that a clinical trial with 2 year follow-up data is not robust (START A, START B, START L and 035). The data were considered robust enough to form the basis of the decision by the European Commission to approve Marketing Authorisation for dasatinib in advanced/blast stage CML following a positive Committee for Medicinal Products for Human Use (CHMP) opinion. In fact, BMS obtained and incorporated advice on the clinical study design from the CHMP where appropriate, prior to starting the trials. For completeness, we include extracts from dasatinib's Summary of Product Characteristics that emphasises the clinical studies of dasatinib in the blast phase and overall survival periods:

> *"Myeloid Blast Phase CML*
>
> An open-label, single-arm, multicenter study was conducted in patients intolerant of or resistant to imatinib. A total of 109 patients received dasatinib 70 mg twice daily (99 resistant and 10 intolerant to imatinib). The median time from diagnosis to start of treatment was 48 months. Median duration of treatment on dasatinib was 3.5 months with 12% of patients treated for > 24 months to date. The rate of major molecular response (assessed in 19 patients with a CCyR) was 68% at 24 months.
>
> *Lymphoid Blast Phase CML and Ph+ ALL*
>
> An open-label, single-arm, multicenter study was conducted in patients with lymphoid blast phase CML or Ph+ ALL who were resistant or intolerant to prior imatinib therapy. A total of 48 patients with lymphoid blast CML received dasatinib 70 mg twice daily (42 resistant and 6 intolerant to imatinib). The median time from diagnosis to start of treatment was 28 months. Median duration of treatment on dasatinib was 3 months with 2% treated for > 24 months to date. The rate of major molecular response (all 22 treated patients with a CCyR) was 50% at 24 months. In addition, 46 patients with Ph+ ALL received dasatinib 70 mg twice daily (44 resistant and 2 intolerant to imatinib). The median time from diagnosis to start of treatment was 18 months. Median duration of treatment on dasatinib was 3 months, with 7% of patients treated for > 24 months to date. The rate of major molecular response (all 25 treated patients with a CCyR) was 52% at 24 months. Further efficacy results are reported in Table 6 (see SPC). Of note, major haematologic responses (MaHR) were achieved quickly (most within 35 days of first dasatinib administration for patients with lymphoid blast CML, and within 55 days for patients with Ph+ ALL).
>
> *Phase III clinical studies in patients with CML [in chronic, accelerated, or] myeloid or lymphoid blast phase[, and Ph+ ALL] who were resistant or intolerant to imatinib*

In patients with myeloid blast phase CML, the median duration of MaHR was 8 months and 9 months for the 140 mg once daily group and the 70 mg twice daily group, respectively; the median PFS was 4 months for both groups; and the median overall survival was 8 months for both groups. In patients with lymphoid blast phase CML, the median duration of MaHR was 5 months and 8 months for the 140 mg once daily group and the 70 mg twice daily group, respectively; the median PFS was 5 months for both groups, and the median overall survival was 11 months and 9 months, respectively."

Indeed, on this basis, one must query how many orphan and ultra-orphan medicines are likely to satisfy the Appraisal Committee's unspecified standards of robustness. Following the Servier case (*Servier Laboratories Limited v National Institute for Health and Clinical Excellence (2010)),* it is clear that NICE must place sufficient weight on evidence that is central to a party's case, particularly when such evidence has been held as being robust enough for marketing authorisation purposes. The failure to do so in this case is unreasonable.

2.4 The Conclusion That Dasatinib Is Not Innovative Is Perverse

The FAD states at paragraphs 4.3.30 that neither dasatinib nor nilotinib represent a "step change" in innovation and did not identify any potential significant and substantial health-related benefits that had not been included in the economic models. We and other consultees (see Novartis' submissions and submissions from the CML Support Group UK) disagree with this view. The CML Support Group UK explain that "There are, as far as we are aware, no publically available NICE criteria deployed to grade the degree of innovation displayed in any particular case and it seems such classificatory work proceeds on an *ad hoc* basis."

Dasatinib is clinically effective for imatinib-resistant patients and fulfils an area of unmet need due to the limited treatment options available to patients in this setting, particularly in the blast phase of the disease.

NICE recognises that imatinib represented a "step change" in the treatment of CML. Imatinib is an oral inhibitor of the ABL kinase and produces durable responses in patients with CML. Based on high rates of both haematologic and cytogenetic responses, imatinib is currently approved for use in newly diagnosed CML patients, as well as in CML blast phase patients previously treated with interferon. However, although imatinib is effective in treating newly diagnosed CML, resistance to imatinib has emerged. The 2-year incidence of resistance is estimated to be 80% in blast phase, 40% to 50% in accelerated phase, and at least 10% in chronic phase.[21]

Dasatinib, on the other hand, represents a significant advance in the treatment of CML and for imatinib-resistant patients in particular. Dasatinib, *in vitro* targets specific sites of the protein kinase family, inhibiting the activity of the BCR-ABL kinase in addition to other kinases Dasatinib, has also been demonstrated *in vitro* to be a potent, sub-nanomolar inhibitor of the BCR-ABL kinase with potency at concentration of 0.6-0.8 nM. It binds to both the inactive and active conformations of the BCR-ABL enzyme.

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[21] Dasatinib, European Public Assessment Report. See http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000709/WC500056995.pdf, last accessed 15 August 2011.

Both patients and clinicians recognise and appreciate the added therapeutic option that dasatinib provides and we consider that a failure to take account of the innovative nature of dasatinib is perverse.

2.5 Ultra-orphan

The FAD records at section 2.4 that there are approximately 560 people are diagnosed with CML in the UK each year. We are therefore clearly in ultra-orphan territory, as that term has been defined by NICE in its Social Value Judgements (SVJ) publication,[22] which is binding on NICE.[23]

NICE has recognised that ultra-orphan drugs require special treatment if they are to be meaningfully appraised. For example, on the issue of drugs for rare conditions, the SVJ makes a distinction between its appraisal techniques for appraising "orphan drugs" (drugs for rare conditions) and "ultra-orphan drugs" (drugs for "very rare" conditions). Page 20 of the SVJ states:

> *"NICE considers that it should evaluate drugs to treat rare conditions, known as 'orphan drugs', in the same way as any other treatment (see Glossary).*
>
> *NICE does not expect to receive referrals from the Secretary of State for Health to evaluate 'ultra-orphan drugs' (drugs used to treat very rare diseases or conditions). This is because the Department of Health currently has other mechanisms to assess the availability of ultra-orphan drugs in the NHS."*

There are two possibilities. One, such drugs are not referred, and are instead dealt with under different processes, for example relating to specialist commissioning. Two, if such drugs are referred and the referral proceeds then NICE must approach such drugs differently. Otherwise, as the draft NICE opinion on orphan and ultra-orphan drugs recognises,[24] the result of the appraisal will invariably give rise to values that would be considered cost ineffective under conventional criteria. The draft opinion, which was developed following consultation with the Citizen's Council and in response to a request from the Department of Health, therefore recommends that ICERs in the range £200,000 - £300,000 per QALY may be acceptable for ultra-orphan products.

The opinion may be marked draft, but it cannot simply be dismissed. It has been on the NICE website for some 5 years, was submitted to the Department of Health as representing NICE's view and, we understand, disclosed following a Freedom of Information Act request.

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[22] Social Value Judgements, Principles for the Development of NICE Guidance, 2nd Edition, at p. 36: occurrence rate 1 in 50,000, i.e. less than 1,000 in the UK. Available at http://www.nice.org.uk/media/C18/30/SVJ2PUBLICATION2008.pdf, last accessed 15 August 2011.

[23] The SVJ states at page 3: "*All NICE guidance, and the procedures NICE uses to develop its guidance, should be in line with the Institute's legal obligations and the social value principles set out in this document. If any parts of NICE's guidance do not conform to these principles, NICE and its advisory bodies should identify them and explain the reasons why.*"

[24] See NICE guidance (draft, marked version 3) on appraising orphan drugs, http://www.nice.org.uk/niceMedia/pdf/smt/120705item4.pdf, last accessed 15 August 2011.

Given that the outcome of an appraisal of an ultra-orphan drug will inevitably be a conclusion that it is not cost-effective under conventional criteria, it is perverse for the Appraisal Committee to have ignored dasatinib's ultra-orphan status.

3. The Institute has exceeded its powers

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

NICE has exceeded its powers by making recommendations that are incompatible with certain fundamental freedoms under the European Convention of Human Rights (ECHR), as transposed into national law under the Human Rights Act 1998. In particular, the guidance breaches Articles 2, 3, 8 and 14 of the ECHR for the following reasons:

- the recommendations rob patients in the blast phase of CML to extra life (Art. 2),
- refusing dasatinib to blast phase CML patients with just months to live amounts to inhumane and degrading treatment (Art. 3),
- patients with blast phase CML will usually die within 3-6 months compared with 8-11 months if they are treated with dasatiniband this denies such patients the right of a family life and privacy (Art. 8),
- the recommendation is discriminatory in that it forecloses meaningful treatment to certain groups of patients with blast phase CML for whom stem cell transplantation is not an option (i.e., the elderly), or for whom there is a very limited donor pool (i.e. those from ethnic minorities) (Art 14).

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

For the reasons stated in paragraph 1.4 of this appeal letter, we consider that the Institute has exceeded its powers in making recommendations based on a Patient Access Scheme that was submitted and accepted by NICE outside the clear submission timelines set out in the PPRS.

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4. Conclusion

BMS reserves the right to add to and/or elaborate upon these appeal arguments in any oral presentation scheduled with the Appeal Panel. It also reserves the right to put further evidence or arguments before the Appeal Panel, within the guidelines set out in the Institute's Guidance to Appellants.

We look forward to the Appeal Panel's response in due course.

Yours sincerely

Maximilian Lebmeier
Associate Director Health Economics & Outcomes Research

Enclosures: Appendix 1: Observations on PenTAG / SHTAC Modelling

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Appendix 1: Observations on PenTAG / SHTAC Modelling

Unless otherwise stated, all references to any economic model in this appendix refer solely to the SHTAC modification of the PenTAG model.

- The model allows for individuals to spend longer in one health state than they do alive, and uses inconsistent approaches to modelling key parameters for different drugs (implicitly stating that they act in a biologically different manner).

- The approach allows for individuals on the older, less effective, interventions to have a lower rate of disease progression than those on newer and more effective drugs.

- In place of high-dose imatinib as the key comparator, the Appraisal Committee has chosen to shift its focus to the use of hydroxycarbamide, despite it representing obsolete clinical practice, as made clear by clinical expert submissions during the course of this appraisal.

- The SHTAC did not include an update of a pivotal study of dasatinib (i.e the dose-ranging study BMS-034). The PenTAG and the SHTAC assessment reports only included the 6-month follow-up data of this study, and not the 2-year[25] and 4-year[26] follow-up data that we made clear (in our response to the ACD.) should have been included. The failure to take account of such relevant evidence is perverse, particularly when the Appraisal Committee suggests that what it regards as the limited evidence has influenced its recommendations.

- The SHTAC model report "did not address imatinib intolerance",[27] nor does any of the data discussed in the FAD refer to intolerant patients. Therefore the recommendations, regarding imatinib-intolerant patients, which are based on the SHTAC analysis, are even more uncertain that those of the imatinib-resistant population. Further, the Appraisal Committee suggests that effectiveness is "likely to be greater in intolerant patients" and that dasatinib is "likely to be as least as cost effective". These comments do not appreciate or reflect the magnitude of additional clinical benefit seen in these patients for whom response rates (CCyR and MCyR) at 2 years are approximately 20% higher than those seen in imatinib resistant patients.

- The SHTAC model disregarded the overall treatment costs that should include much more expensive and more complicated post-failure treatments such as bone marrow stem cell (BMSCT) transplantations, while the AC disregarded the BMS ongoing monthly costs associated with ongoing care post BMSCT of £2400 (a figure supported by HCIS Comments) and the reduced health utility this represents. This is supported by the comment from the

[25] Shah NP et al (2008a) Dasatinib Dose-Optimization in Chronic Phase Chronic Myeloid Leukaemia (CML-CP): Two-Year Data from CA180-034 Show Equivalent Long-Term Efficacy and Improved Safety with 100 Mg Once Daily Dose. ASH 2008 Poster Number 3225

[26] Shah NP, Cortes JE, Schiffer CA et al.. Four-year follow-up of patients with chronic-phase chronic myeloid leukaemia (CP-CML) receiving 100 mg of dasatinib once daily. J Clin Oncol 2010a;28:15s(suppl):abstr 6512.

[27] Paragraph 4.1.2 of the FAD.

RCN which stated that the ongoing complications at 3, 6, 12 months and beyond are not addressed in the ACD. In addition, as stated previously, based on expert guidance, only a very small proportion (5-15%) of CML patients are likely to be able to receive BMSCT.

- The model also contained a number of perverse issues and errors concerning the use of surrogate markers of efficacy and treatment duration assumption

Surrogate markers

- There was no link in the PenTAG/SHTAC model between MCyR and PFS, so any increase in the MCyR values would have no impact on PFS. Given the well established link between CCyR and PFS it is difficult to believe that the assumption of no link between MCyR and PFS is correct (early data suggests this is not the case[28])

- The rates of CCyR and MCyR used in the FAD are incorrect – they refer to imatinib resistant patients only and do not take into account the published 2 year data for dasatinib (44% CCyR and 59% MCyR for the resistant population) for the licensed dose[29]. Perversely, despite criticism from the AC that this was the only study to use the licensed dose, it nevertheless is not fully taken into account. Further, the AC acknowledge clinical opinion that the efficacy of dasatinib is likely to be better in real life practice an opinion that has recently been supported by data from a BMS observational study showing 'real world' CCyR rates of 58% for imatinib resistant patients.

- There are no CCyR or MCyR rates reported in the FAD for imatinib intolerant patients.

- The Appraisal Committee noted that surrogates were required to predict overall survival (OS) due to the short duration of the studies. However, this is not entirely accurate, as even after 5 years follow up of dasatinib patients median OS has not been reached. The correct interpretation is that surrogates are necessary due to the long median OS exhibited by patients treated with dasatinib, which further reinforces the clinical benefit of dasatinib treatment.

Treatment duration

- The SHTAC AG seemed to be unable to model treatment duration and so, instead, simply used 'plausible' estimates. The AC did not agree with these estimates and instead asked for further analysis based on the estimates of treatment duration that the AC believed were plausible – see below – and not based on disease modelling. Treatment duration should be based on PFS (as patients will generally not be treated

[28] Milojkovic, D et al (2010) Early prediction of success or failure of treatment with second-generation tyrosine kinase inhibitors in patients with chronic myeloid leukemia. Haematologica 2010: 95: 224-31.

[29] Shah NP et al (2008a) Dasatinib Dose-Optimization in Chronic Phase Chronic Myeloid Leukaemia (CML-CP): Two-Year Data from CA180-034 Show Equivalent Long-Term Efficacy and Improved Safety with 100 Mg Once Daily Dose. ASH 2008 Poster Number 3225

past this point), which should in turn be reflected in increased overall survival (OS). However, the SHTAC analysis divorces improved PFS from improved OS – so by extending the PFS the only thing the analysis achieves is to extend treatment duration and increase costs, with no commensurate improvement in outcome. In the words of Jane Apperley 'By altering these parameters and by choosing an effective but exceptionally inexpensive comparator, hydroxycarbamide, the QALY became unacceptably large and it was on this basis that the decision was reached'

- A fundamental and logical principle of the SHTAC model is that the treatment duration for a given intervention arises as a consequence of the choice of a range of other model parameters and hence is an **output** and not an **input (driver)** of the model. SHTAC have perversely chosen an arbitrary treatment duration as a direct entry into their economic model in order to produce a result which suits their preconceived position. Further, the model has been recoded post completion and submission in order to accommodate this arbitrary treatment duration. Inputting another treatment duration would produce a different output – which could be repeated *ad nauseum*, – rendering this modelling approach meaningless.

- The arbitrary decision by the AC to set a treatment duration of 10 years in the SHTAC analysis, in order to produce what AC refers to as "the least implausible analysis", is based on the AC's view that >50% patients receiving these therapies are likely to do so for more than 10 years. However, this is not evidence based, as for instance, dasatinib trial data show only 35% patients are still receiving treatment at 5 years[30]

[30] Shah, NP et al (2011) Five-year follow-up of Patients with Imatinib-Resistant or –Intolerant Chronic-Phase Chronic Myeloid Leukemia (CML-CP) Receiving Dasatinib. Presented at the American Society of Clinical Oncology 2011, Jun3-7, Chicago, IL.