Appraisal Committee comments on the submissions from Bristol Myers Squibb on the application of articles 2, 3, 8 and 14 of the European Convention on Human Rights to the Committee's guidance on the use of dasatinib for CML patients in the blast phase who are imatinib-resistant or intolerant

1. The Committee understands and accepts that the Institute is bound by the Human Rights Act and European Convention on Human Rights (ECHR). The question as the Committee understands it is whether any of the Convention rights are engaged or breached by the decisions taken in this appraisal.

2. The decision of the Appeal Panel in the Azacitidine appraisal was published during the course of this appraisal. While the Committee understands that the Appeal Panel in this case is not bound to follow the Azacitidine decision as a precedent, it has proceeded on the basis that the view of the Azacitidine Appeal Panel on the scope of articles 2, 3 ,8 and 14 (which was not subject to further legal challenge by the appellants) was correct.

<u>The effectiveness of dasatinib as a blast-phase treatment for imatinib-resistant and imatinib-intolerant patients</u>

3. The Committee believes that a clear understanding of the nature of its findings on the clinical and cost effectiveness of dasatinib in the blast phase is essential as background to its submissions on the ECHR points raised by Bristol Myers Squibb (BMS). In relation to dasatinib in the blast phase of CML the appraisal found an indication of some gain to patients, a low quality evidence base and very high costs.

4. Patients in the blast phase of CML are in a terminal phase of the illness. Any treatment provided to them at this stage can, at best, only prolong life and not save life. The references in BMS's submission to cases concerning treatments that save lives or avoid risks to health and references to patients in a "life or death" or "life-threatening" situation [paragraphs 5, 8 10, 13, 26 of the BMS submission] are not relevant to the use of dasatinib in blast-phase CML.

5. In addition the Appraisal Committee considers that the references in BMS's submissions to dasatinib as an "effective treatment" or as providing "significant extension of life" [paragraphs 7, 19, 20, 23, 26] substantially over-state the evidence of the clinical effectiveness of dasatinib in the blast phase of CML. Even on BMS's own modelled analysis as submitted to the Appraisal Committee (Table 63, page 131, BMS II/IR submission, and Table 32, page 82 of BMS IR submission), the model outcomes showed that dasatinib prolonged life by around 5 - 6 months on average compared with other treatments (translating to a quality adjusted life gain of 2-3 months). BMS now state in paragraphs 7 and 23 of its submission that dasatinib prolongs life by up to an additional 8 months, but it should be noted that this must be the maximum gain obtained by any patient and not the average gain. While some patients may gain up to 8 months equally others will gain less than the average of 5-6 months. However the Committee considered that the evidence base even for a benefit of 2-3 months quality adjusted life gain was weak, in terms of the small amount of data available and the quality of that data which was gained from uncontrolled studies. This is different from the findings on azacitidine, where the Committee accepted that there was evidence that azacitidine prolonged life by around 9 months on average (not up to a 9 month maximum).

6. In the terminal phase of any condition the options for treatment inevitably diminish and any treatments provided are aimed at prolonging and not saving life. The options for treatment in the blast phase must be considered in this context. The Committee does not accept the statement of BMS that failure to recommend dasatinib in itself leaves patients in the blast phase without any treatment (see BMS paragraph 21 "*If the FAD were adopted, all blast-phase CML patients (for which no other similarly effective treatment is licensed) who are not already being treated with dasatinib would be moved to a situation where treatment would not be provided*"). For patients who cannot have imatinib or stem cell transplantation, treatment is determined on the basis of an assessment of the individual patient. Best supportive care is

provided to all patients in addition to any other medication provided, and in the context of the NHS this simply cannot be regarded as "no treatment".

7. The Committee fully recognises that any extension of life is of enormous value to patients and their families, particularly where a particular treatment offers greater quality of life during the extended period . That value has been taken into account in the Committee's considerations.

8. The QALY is a tool which enables NICE to compare benefits gained from medicines across different treatments and conditions and captures benefits such as extension of life and quality of life during the extended period. The "cost per QALY" gained for a particular treatment such as dasatinib is calculated by dividing the cost difference between dasatinib and the appropriate comparator treatment, such as best supportive care, by the full health benefit that dasatinib brings to patients, including both the additional months gained and the quality of life in those months. In this calculation the life extension is valued in the same way as comparable benefits (including life extensions) achieved by other treatments. The cost per QALY is therefore a figure for the cost per benefit, not a nominal figure for baseline cost or cost of the treatment to the NHS.

9. The Appraisal Committee was not able to identify a reliable cost per QALY for the use of dasatinib in the blast phase, because the evidence base was too weak. This is an unusual situation within an appraisal process. However the Committee carefully examined the evidence that was submitted by BMS and was able to reach an overall view on the costs of dasatinib in the blast phase and how these were likely to compare to the level of cost per QALY at which treatments are generally considered to be cost effective. The BMS submissions (Table 63 page 131, BMS II/IR submission, and Table 32, page 82 of BMS IR submission) contain figures based on two uncontrolled studies of the use of dasatinib in the blast phase. These figures show that dasatinib resulted in an average of less than 6 months survival extension. Modelling by BMS on the basis of these figures shows an approximate quality adjusted life gain of 2-3 months compared to imatinib (which those patients have failed). BMS's own figures also show that the costs of dasatinib treatment in the blast phase would be at least £80,000. On the basis of these figures the Committee was well aware that any cost per QALY gained for dasatinib in the blast phase would be likely to be several times higher than the range of £20,000 to £30,000 per QALY gained at which treatments are normally considered to be cost-effective.

10. Therefore it was clear to the Committee that the available evidence indicates that the benefits achieved by dasatinib, i.e. extension of life, are likely to cost at least twice and possibly many times as much as the same benefits (including similar length extensions of life) achieved by treatments that are normally considered to be cost-effective uses of NHS resources.

Anxious scrutiny/perversity

11. The Committee notes the argument in paragraphs 5 and 6 of BMS's submissions that the Panel should approach the perversity grounds of the appeal with rigorous or anxious scrutiny because this is a case of interference with human rights. For the reasons set out below, the Committee does not accept that this is a case in which its decision interferes with human rights. It also notes that the case of R (Rogers) v Swindon NHS PCT, quoted in paragraph 5 of BMS's submissions, was concerned with potentially life-saving treatment that was being denied on the basis of an individual funding decision relating to a single patient, rather than with guidance on the general availability of potentially life-prolonging treatment.

Articles 2 and 3

12. It is the Appraisal Committee's understanding that, as stated in the Azacitidine appeal decision, the ECHR case law simply does not indicate that national guidance on the general availability of a particular medical treatment engages the rights in articles 2 and 3 ECHR.

13. The Committee notes BMS's arguments that this is not an absolute position and that articles 2 and 3 will be engaged by decisions on specific medical treatments in particularly serious

cases (paragraph 10 of the BMS submission). The Committee comments firstly that it is not clear that the cases cited by BMS do contain any clear indication that articles 2 and 3 apply to a general recommendation that seeks to ensure appropriate distribution of resources within an established national health service that offers a consistent high standard of care that is free at point of use, as compared to individual decisions on treatment. Secondly the Committee considers that BMS's argument that the guidance on dasatinib is within any exceptional category that could engage articles 2 and 3 are in any event flawed.

14. The exceptional category is said to cover cases where the patient's life is at stake. However in relation to the use of dasatinib in the blast phase the following must be considered:

    - this is not a life-saving treatment but a treatment for patients in a terminal phase of illness, in which treatment options are inevitably limited due to the condition itself rather than due to the Institute's guidance;

    - all patients in the blast phase will be considered for any alternative treatment options, on the basis of their individual suitability, and all patients receive best supportive care. In the context of the National Health Service this cannot be regarded as leaving patients without any medical treatment or care;

    - extent of the benefit actually provided by the treatment

15. As regards the benefit of the treatment, the Committee accepted that the evidence that is available indicates that dasatinib provides benefit through extension of life in the blast phase. However for the great majority of the patients in the blast phase it is at least doubtful whether that can be regarded as so significant as to place dasatinib in an exceptional category of treatments to which articles 2 and 3 apply. As indicated above, the evidence base for dasatinib in the blast phase was very weak. However BMS's own data indicated an average extension of less than six months of survival, modelled to less than 3 months quality adjusted life gain compared to the control treatments. The reference in paragraph 23 of the BMS submissions to "up to 8 additional months of life" must refer to the maximum obtained by any individual patient and should not be read as referring to an average gain or a gain likely to be obtained by individual patients. While the benefit obtained from dasatinib is of undoubted value to patients and their families, there is no indication that the size of that benefit puts this treatment in an exceptional category compared to other life-prolonging or life-saving treatments so as to engage articles 2 and 3 ECHR. The arguments for applying articles 2 and 3 to a negative recommendation for dasatinib are in fact much weaker than those for applying articles 2 and 3 to a negative recommendation for azacitidine, which was accepted as giving patients around 9 months of additional life on average.

16. In addition, BMS's argument that article 2 is relevant is based on the idea that the position of the patients "can be remedied in a proportionate manner" [paragraph 10 of the BMS submission]. The evidence on cost suggests that the cost of providing dasatinib is not proportionate to the benefit gained and overall would not represent an effective, proportionate use of NHS resources. The Committee appreciates that the overall number of patients who would receive dasatinib in the blast phase is relatively small, but the use of NHS resources to provide the treatment is still likely to displace several times more equivalent benefits for other patients, who may well also be suffering from life-threatening or terminal conditions. This cannot be regarded as a proportionate measure.

17. Overall the Committee does not accept that in this context articles 2 and 3 are engaged by a recommendation as to the general availability of one particular treatment option which is of uncertain efficacy in the blast phase.

18. The Committee notes the arguments put forward by BMS with regard to ultra-orphan drugs and the obligation of a state to take steps to safeguard lives. The Committee would like to point out firstly that the appraisal topic is for all phases of CML (chronic phase, accelerated phase and also blast phase). The Committee heard from clinical specialists that ' *treatment with dasatinib, high-dose imatinib and nilotinib is given in accordance with European guidelines...., that more than 50% of people with imatinib-resistant CML treated with dasatinib*

or nilotinib have a good response to treatment and... these patients would receive dasatinib or nilotinib treatment for the rest of their lives, and possibly have a nearly normal life expectancy (that is, at least 10 more years)' [See FAD sections 4.3.5 and 4.3.6]. '*It is estimated that about 560 people are diagnosed with CML in the UK each year* ' [see section 2.4 of FAD]. Therefore, dasatinib cannot be considered as an 'orphan drug'. Secondly in the NICE social value judgements paper (second edition), page 20, section 4.4 (tab 17 of appeal papers) it is stated: '*Rare conditions*: *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.'* The appraisal topic referred to NICE by Department of Health is for all phases of CML (chronic phase, accelerated phase and also blast phase) and has not therefore been considered as an 'orphan drug'.

19. More generally, given the factors set out in paragraph 14 above the Committee considers that a negative recommendation of dasatinib does not constitute a failure to safeguard lives.

20. In relation to article 3 specifically, the Committee does not agree that the D v UK case demonstrates that article 3 is relevant to NICE recommendations. That case concerned positive action to remove an individual patient from access to treatment which was generally available to patients in the UK, whereas the Committee is giving a general negative recommendation as to future availability of a particular treatment within a comprehensive national health service (with patients currently receiving the treatment continuing to do so as long as their clinicians consider this appropriate). In addition, the effect of the decision on D was to place him within an entirely different health service with uncertain treatment options. Patients in the UK with blast-phase CML all retain access to extensive NHS treatment resources, with consideration of other medical treatments and provision of best supportive care. This is certainly not equivalent to withholding medical treatment or otherwise subjecting patients to inhumane or degrading treatment.

21. The Committee considers that the final sentence of paragraph 20 of the BMS submission ("The present case falls into the exceptional group of cases where the benefits of the treatment are sufficiently established and the effects of denying treatment so severe, that Article 3 is engaged and is violated") is inaccurate on two counts: (1) as to the extent to which the benefits of the treatment are established in blast phase compared to other life-prolonging or saving treatments; and (2) as to the severity of the effects of denying treatment, where the impact of dasatinib is compared even with best supportive care alone. The Committee strongly rejects the idea that best supportive care within the NHS can be regarded as "inhuman and degrading treatment" within article 3.

Article 8

22. The Appeal Panel in the azacitidine appraisal accepted in principle that article 8 may be engaged in relation to decisions on medical treatment but considered that a high threshold applied as to when a decision not to provide treatment would constitute a breach of article 8. The Committee shares the view that article 8 will only very rarely be breached by a decision on medical treatment. The Committee considers that there is no indication that the decision on dasatinib falls into that rare category, given the factors set out above regarding the nature of the recommendation, the nature of the condition and the evidence as to clinical effectiveness and cost.

23. Even if the Committee's recommendation has breached article 8(1), the Committee considers that the breach would be justified under article 8(2) because it is necessary with regard to the protection of health and morals, or for the protection of the rights and freedoms of others. This is on the basis of the need to allocate limited public resources only to cost-effective medical treatments, in the context of the state's limited resources and the provision of a comprehensive healthcare system that is free at the point of access. The underlying principle is that for the population as a whole it is best to get as much health benefit as possible with

the resources available. NICE was established to address this by assessing clinical and cost effectiveness. It is inherent in NICE's role that there will be treatments that provide some clinical benefits to patients but which cannot be recommended for general use in the NHS because they are not cost-effective.

24. The Committee refers to paragraphs 7 to 10 and 15 above in which they set out the way in which the costs and benefits of dasatinib have been identified and taken into account. If the Committee were to recommend dasatinib on the basis of the existing evidence base, then the effect would be to reduce the overall health benefit within the population because money used to fund dasatinib in the blast phase is likely to displace at least twice and possibly several times more of the equivalent benefit provided by treatments shown to be cost effective. In other words, if one person benefits from dasatinib, then two or more other people lose the equivalent benefit, which may include comparable extensions to their lives. On this basis the committee's negative recommendation of dasatinib is necessary to protect the overall health of the population.

Article 14

25. As set out above the Committee does not accept that articles 2 and 3 are applicable to its recommendation and therefore it does not accept that article 14 is engaged in that context. The Committee accepts that article 8 may be engaged and accordingly that article 14 may be engaged in respect of the article 8 rights.

26. The Committee agrees with the view of the Appeal Panel in the azacitidine case that the relevant right or benefit in respect of which there may have been discrimination is the right to access the particular treatment in question, i.e. dasatinib, rather than the right to access treatment generally for the condition in question or the right to a particular outcome from treatment, particularly where it is concerned with a treatment phase which is solely focused on extending life and not on curing or saving life. There is no less favourable treatment for a particular group as all patients are treated equally in respect of access to dasatinib.

27. The Committee would also query whether the group of patients in the blast phase constitutes a particular age group which is being treated differently by virtue of its age, where the reason that people in that group tend to be older than those in the other phases of CML is simply that the disease progresses over time.

28. Even if the Panel considers that there is indirect discrimination because the Committee's recommendation impacts disproportionately on older patients and those of certain ethnic family origins, the Committee would argue that any indirect discrimination is justified as being a proportionate means of achieving a legitimate aim. The legitimate aim is the objective of cost-effective use of NHS resources. The Committee argues that a negative recommendation of dasatinib is a proportionate means of achieving this aim on the basis of the factors set out above in terms of the extent of the benefit obtained by patients, the strength of the evidence for that benefit and the fact that the value of the extension to patients' lives has been taken into account through the cost effectiveness calculations.

Equality Act 2010 and the Public Sector Equality Duty

29. The Committee notes that BMS reserves its position as to whether there has been a breach of the Public Sector Equality Duty in the Equality Act 2010.

30. The Committee confirms that it gave careful consideration to the equalities impact of its decisions, in the following way:

    - throughout this appraisal, potential inequalities in the impact of the Committee's work have been considered and equality impact assessments carried out in respect of the guidance [three ACDs and FAD] The technology appraisal process provides for EIAs to be published when the final guidance is published. However the considerations

within the EIAs are also reflected in the FAD and the ACDs and were considered at all Appraisal Committee meetings.

- there has been full consideration of the impact of a negative recommendation on all patients, including patients with protected characteristics, in the course of analysing the clinical and cost effectiveness of the treatments within the FAD;

- the analysis in paragraph 4.3.31 of the FAD, which is not a "summary treatment" of equalities issues having regard to the fact that the Committee considered that impact on protected groups arose from the condition itself and restrictions on other treatments, and having regard to the Committee's view that the clinical effectiveness of dasatinib was limited and not backed by strong evidence.

31. Paragraph 4.3.31 clearly demonstrates that the Committee was aware of the limitations on treatment options for some groups of patient and considered whether its recommendation should be adjusted accordingly. Overall, the Committee was fully aware of the fact that treatment options are limited for certain groups of patient in the blast phase, due to protected characteristics and also co-morbidities and considered whether this required it to review or alter its recommendations in order to have due regard to the need to eliminate unlawful discrimination and promote equality of opportunity. However the Committee considered that the limited availability of some other treatments would not in itself justify the general positive recommendation of a treatment that is not cost effective and is of limited proven clinical effectivenessand where a range of clinical options would still be considered in relation to individual patients on the basis of risk and benefit to them. The Committee believes that this represents due regard under the Equality Act 2010.

20 October 2011