Bristol-Myers Squibb Pharmaceuticals Limited

Uxbridge Business Park, Sanderson Road, Uxbridge, Middlesex UB8 1DH
Tel 01895 523000 Fax 01895 523010

03 October 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

We refer to your initial scrutiny letter of 12 September 2011 requesting that we set out argument under Ground 2.1 (the SHTAC model outputs) in terms that an informed but non-expert panel can understand and that we provide written submissions on Ground 3.1 (human rights).

On both points, we understand your concern that the Appeal Panel may struggle to process all of the arguments if they are only explored orally, due to the technical and/or legal nature of the submissions. We have therefore expanded our argument under Ground 2.1 below and hope that this provides the appeal panel with further clarity and understanding of the issues.

We appreciate that, as in many cases, the submissions on economic modelling are in places technical in nature. However, we strongly consider that it will assist the Panel if we explain and clarify some of the key issues at the appeal hearing itself. This can, in our legal advisers' experience, give the Panel assistance which it is simply not possible to provide in writing.

We note that the Appeal Panel will not have access to expert advice on these issues. However, BMS will be accompanied by , Consultant Haematologist at University Hospitals Birmingham NHS Foundation Trust, who will be able to assist the panel on whether the clinical assumptions that were built into the modelling are sound. , a health economist, will also be on hand to explain the modelling on behalf of BMS.

Bristol-Myers Squibb Pharmaceuticals Limited

Uxbridge Business Park, Sanderson Road, Uxbridge, Middlesex UB8 1DH
Tel 01895 523000 Fax 01895 523010

In the most summary terms, what we wish to convey to the Appeal Panel is that the model relied upon by the Appraisal Committee in making recommendations to the NHS: (1) does not reflect clinical reality; (2) does not reflect the overall cost and benefits of treatment; (3) is based on a misunderstanding of the relevant evidence; and (4) incorporates arbitrary treatment duration parameters. In our view, the flaws in the modelling mean that the Appraisal Committee cannot rationally assess the cost-effectiveness of dasatinib or any other technology, a point made clear by the court in *R (on the application of Ross) v West Sussex Primary Care Trust.*[1] One of the challenges in articulating these points is that BMS itself has not been able to understand fully the modelling because we were not provided with a fully executable version of the model. We are also very concerned that the quality of the modelling used in this appraisal where it has moved from being 100% robust (see the description of BMS's model in Appendix 3 below) at the beginning of the process, to relying on the Assessment Group's model that is recognised as lacking face validity.

For the avoidance of doubt, this expanded version of Ground 2.1 does not address in full the reasons why the underlying data relied on by BMS were in some respects wrongly criticised in the FAD. BMS will develop those submissions as set out in its other Grounds of Appeal. This letter should also be read in conjunction with section 2.4 of BMS's response to the ACD dated 27 May 2011 (enclosed) that provides additional comment.

Our more detailed submission under Ground 3.1 has been prepared by , who will appear as BMS's legal advisor at the oral hearing. This submission is enclosed with this letter.

We look forward to discussion of these points with the Appeal Committee.

Yours sincerely

Associate Director, Health Economic and Outcomes Research

[1] [2008] EWHC 2252 (Admin) at paragraphs 88-92. In that case, the court held that a PCT had acted irrationally in not providing a treatment to a myeloma patient due to the PCT review panel's misinterpretation of the clinical evidence; a failure by the review panel to understand treatment duration, a failure by the review panel to take account of certain costs, and a misunderstanding of treatment response rates and overall survival.

Bristol-Myers Squibb Pharmaceuticals Limited

Uxbridge Business Park, Sanderson Road, Uxbridge, Middlesex UB8 1DH
Tel 01895 523000 Fax 01895 523010

Appendix 1

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

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.

The Appraisal Committee confirmed in paragraph 4.1.19 of the FAD that none of the economic models had presented a plausible ICER, However, the Committee decided to accept 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. Making recommendations based on such flawed modelling is perverse given the clear NICE guidance on modelling in the Guide to the Methods of Technology Appraisals (NICE 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. Appendix 1 of our appeal letter of 2 September 2011 included a number of key areas that either individually or cumulatively led to a perverse decision by the Appraisal Committee to make recommendations to the NHS based on the SHTAC modelling. As requested, we have expanded on these points below (see Appendix 2 of this letter).

The key issue, however, is that the Appraisal Committee made no effort 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 inputs. This was the consensus view of the Appraisal Committee, BMS, SHTAC and clinical opinion. 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 way in which the Appraisal Committee has selected a flawed model is perverse. This is compounded by the availability of models submitted during the appraisal that meet a higher standard in terms of good practice in economic

modelling. The original PenTAG Assessment Report[2] 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 (see Appendix 3 to this letter). BMS's model was reported as being 100% compliant with both the NICE reference case and the structural component by PenTAG.

The checklists show clearly that the models submitted by BMS were consistently considered by PenTAG to be robust from a disease modelling perspective as well as methodologically sound. Where the models were criticised was in relation to the data inputs selected, in other words, the specific values of some of the parameters used.

By contrast, the PenTAG/SHTAC models have fundamental structural flaws, especially due to the inability to model the disease process accurately (see expanded arguments in Appendix 2 below). This difference between challenged data inputs and fundamental structural flaws in the model was perversely overlooked in the FAD.

Against this background, the Appraisal Committee's choice of model clearly represents a decision that is unreasonable and has led to the Appraisal Committee making perverse recommendations to the NHS.

[2] 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

Bristol-Myers Squibb Pharmaceuticals Limited

Uxbridge Business Park, Sanderson Road, Uxbridge, Middlesex UB8 1DH
Tel 01895 523000 Fax 01895 523010

Appendix 2

Expanded Arguments from Appendix 1 of our Appeal Letter

Observations on PenTAG / SHTAC Modelling

Unless otherwise stated, all references to any economic model in this section refer solely to the SHTAC modification of the PenTAG model. In addition to our appeal letter dated 2 September 2011, we also refer the Appeal Panel to section 2.4 of BMS's response to the Appraisal Consultation Document (enclosed), which explored in detail some of the flaws in the Assessment Group's modelling.

Misinterpretation of Evidence Relating to the Disease

The model is based on fundamental misinterpretations of the disease and its treatment and lacks validity when compared with BMS's model.

- When the model is set up to use a ten year treatment duration (i.e., as used for generating ICERs used in the FAD) it allows for individuals to spend longer in one health state than they do alive. In the original model - whereby treatment duration is not defined for each patient - inconsistent approaches to modelling key parameters for different drugs are used (implicitly stating that they act in a biologically different manner). The key example being spending longer in one of the health states used to represent the underlying disease, e.g., spending eight years in the chronic phase of CML and not receiving treatment when the clinical evidence is clear that a patient with CML does not live that long. In either scenario, use of the model will plainly lead to erroneous conclusions and unreliable ICERs. Without major reconstruction it is impossible to quantify the magnitude of these errors but both clearly go against points 3.1.3 and 3.2.3 of NICE's Methods Guide.

- In place of high-dose imatinib as the key comparator, the Appraisal Committee has chosen to shift its focus to the use of hydroxycarbamide (HU), despite it representing obsolete clinical practice, as made clear by clinical expert submissions during the course of this appraisal. The model therefore fundamentally misinterprets the disease and its treatment, and so, by virtue of not comparing the new interventions with what is used in routine clinical practice, the ICERs generated are unreliable from the perspective of deciding what interventions should be funded from the constrained NHS budget. The Appraisal Committee should instead have relied upon a model with higher face validity (i.e. constitutes a better reflection of routine clinical practice, namely the BMS model). Had it done so, when allowing for inevitable uncertainty in all input parameters dasatinib would be considered cost-effective under the normal criteria stated in the NICE reference case. We attach a summary of ICERs generated by all models, including the BMS model (see Appendix 4), for the Appeal Panel's convenience.

In the BMS base case, treatment with dasatinib dominates treatment with high-dose imatinib, i.e., it is more effective and less costly, and in a scenario analysis requested during the appraisal, dasatinib compared to hydroxycarbamide (HU) results in an ICER of £27,932.

- The approach used to model a key clinical parameter (the rate of progression to third line treatment from the chronic to accelerated/blast stages of the disease) allows for individuals on the older, obsolete interventions (such as interferons, HU, etc.) to have a lower rate of treatment progression than those on newer and more effective drugs. This is completely unrealistic from a clinical perspective as the evidence clearly shows that the speed at which a patient progresses from second to subsequent lines of therapy through the chronic, accelerated and blast phases is much slower when using newer drugs, such as dasatinib, compared with older, obsolete drugs. The impact on the ICER is again hard to quantify without major reconstruction work. From a clinical perspective, however, progression to third line therapy would constitute a range of treatment options including acute myeloid leukaemia-style chemotherapy and stem cell transplantation, both of which are more expensive than treatment with either hydroxyurea or interferon. This approach therefore underestimates the cost in the comparator arm and hence generates clinically unreliable and unduly high ICERs.

The Model Failed to Include Key Evidence

- 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 and 4-year follow-up data that we made clear (in our response to the ACD) should have been included. It is of fundamental importance to use information from the maximum follow up period possible in the economic model. 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.

- According to paragraph 4.1.2 of the FAD, the SHTAC model report "did not address imatinib intolerance". Nor do any of the data discussed in the FAD refer to intolerant patients. The model therefore fails to take account of or to incorporate any evidence that would differentiate this patient population from those who develop resistance to first line treatment. The Appraisal Committee merely suggests that the effectiveness of dasatinib is "likely to be greater in intolerant patients" and that dasatinib is "likely to be as least as cost effective". However, this attempt by the Appraisal Committee to extend its flawed conclusions in the imatinib-resistant population to the imatinib-intolerant population is not evidence based, as there has been absolutely no meaningful analysis of the intolerant group. We would like to make the committee aware that resistance would likely become apparent many years after treatment inception

whereas intolerance would become apparent very quickly. Hence, both the patient demographics and disease duration will likely differ in the two groups. Any conclusions for the imatinib-intolerant population are therefore doubly flawed and do not reflect the magnitude of additional clinical benefit seen in this group of patients. For example, the clinical response rate to dasatinib in imatinib-intolerant patients are approximately 20% higher at two years compared with those seen in imatinib resistant patients. These data should have been taken into account in the modelling.

- The SHTAC model inaccurately calculated the overall treatment costs in treating patients with CML. Routine clinical practice dictates that these costs should include much more expensive and more complicated post-failure treatments such as bone marrow stem cell (BMSCT) transplantations and the monthly costs of care post BMSCT of £2400 *for all treatment options not just those in the BMT arm of the model* (a figure supported by HCIS Comments). As stated above, without major reconstruction of the SHTAC model it is hard to generate absolute ICERs but it should be clear that any intervention that would delay progression to third line therapy would be discriminated against due to this omission (since more people would likely require this treatment and sooner meaning that the cost of treatment would be greater in the comparator arm). In particular, given that second line HU is likely to have a minimal (at best) clinical impact on CML this effect will be amplified for the comparison with dasatinib since the additional costs will be incurred almost immediately whereas for dasatinib it will be many years into the future. This position is supported by the comment from the Royal College of Nursing, which stated during the consultation process that the ongoing complications of BMSCT at 3, 6, 12 months and beyond are not addressed in the ACD.

The Model inaccurately uses available information on Surrogate Markers of Treatment Efficacy

The model contains a number of perverse issues and errors concerning the use of surrogate markers of treatment efficacy. Information on key clinical parameters (overall survival and progression free survival) in these types of study are based on use of a 'surrogate' or intermediate clinical parameter for which there is long term data. The key clinical marker in CML is complete cytogenic response – CcyR and measuring CcyR can provide an indication of overall survival or progression-free survival. However, another surrogate marker for overall survival and progression-free survival is "major" cytogenic response – i.e., not a complete cytogenic response. However, major cytogenic response was not linked to progression-free survival in the model, only a complete cytogenic response. The consequences of this means that altering the value of major cytogenic responses has no impact on the time spent in progression-free survival in the model. In other words, the amount of time spent on therapy remains constant, which is clinically unrealistic. As an example of this, when using the value for major cytogenic response taken from the Shah paper referred to

above, the ICER changes from £43,816 to £42,800 – showing the very limited impact on the model results despite a significant increase in cytogenic response.

- The rates of CCyR and MCyR used in the FAD refer only to the imatinib-resistant population. The rates do not reflect the imatinib-intolerant population 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.

- The Appraisal Committee noted that surrogate end-points are 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.

The Treatment Duration Values are Arbitrary

The model contains a number of perverse issues and errors relating to treatment duration assumptions.

- The original SHTAC did not include treatment duration among its list of input parameters and in the subsequent *post-hoc* analyses did not correctly model treatment duration. Instead, it incorporated so-called 'plausible' estimates of treatment duration into the model. 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 progression free survival (as patients will generally not be treated 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.*'

- The decision by the AC to set an arbitrary 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, there is no evidence for this treatment duration. Clinical trials of dasatinib show that only 35% patients are still receiving treatment at 5 years. [Consideration should have been given to including a stopping rule based on clinical trial data and expert opinion.]

- A fundamental and logical principle of the original SHTAC model is that treatment duration is NOT a model input (i.e. something which can be defined by

Uxbridge Business Park, Sanderson Road, Uxbridge, Middlesex UB8 1DH
Tel 01895 523000 Fax 01895 523010

the user which then feeds into the model) for a given intervention but instead arises as a consequence of the choice of a range of other model parameters and hence is an ***output*** from 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. No meaningful consideration was given to a stopping rule. Further the model has been recoded post completion and submission, in order to accommodate this arbitrary treatment duration. The approach they have used, however, is to vary the treatment duration but not overall survival. The result of this approach results in the 'more in a health state than alive' problems discussed above. By ignoring fundamental modelling principles it is possible to generate any desired ICER using the SHTAC model - inputting another treatment duration would produce a different output – which could be repeated ad nauseum, – rendering this modelling approach meaningless.

Bristol-Myers Squibb Pharmaceuticals Limited

Uxbridge Business Park, Sanderson Road, Uxbridge, Middlesex UB8 1DH
Tel 01895 523000 Fax 01895 523010

Appendix 3
Appraisal of economic evaluations in industry submissions: checklists[3]

Tables 115 through 120 below show the review undertaken by PenTAG in their original assessment reportof the BMS model according to the NICE reference case and a commonly used critical appraisal checklist.

The reviews consider the chronic phase of the disease separately from the accelerated phase and the blast crisis phase. Tables 115, 117, and 119 show that on all items the BMS model(s) met the criteria for the NICE reference case. Tables 116, 118 and 120 show the PenTAG review of the BMS model(s) according to the Philips checklist. The checklist is an in-depth assessment of a model and considers the adequacy of its structure, the data sources used, and its consistency. Importantly, all three tables show the BMS model scored 100% in terms of the structural evaluation with criticisms confined to the data inputs chosen and consistency.

TABLE 115 *Manufacturer submission for dasatinib (chronic phase) – comparison with the NICE reference case*

NICE reference case requirement		Reviewer comment	
Decision problem	As per the scope developed by NICE (eso. technologies & patient group)	✓	Treatment with dasatinib of adults with CML resistant or intolerant to previous treatment including imatinib. Imatinib-intolerant patients were not considered separately.
Comparator	Alternative therapies routinely used in the UK NHS	✓	Imatinib (600 and 800mg/day) and nilotinib. Other comparators included in the scope (hydroxycarbamide, IFN and acute leukaemia chemotherapy) were not included in the analysis as not considered relevant.
Perspective on costs	NHS and PSS	✓	
Perspective on outcomes	All health effects on individuals	✓	
Type of economic evaluation	Cost-effectiveness analysis	✓	
Synthesis of evidence on outcomes	Based on a systematic review	✓	
Measure of health benefits	QALYs	✓	Life years gained were also measured.
Description of health states for QALY calculations	Use of a standardised and validated generic instrument	✓	A cross sectional study was commissioned to calculate utility values. The impact of serious adverse events on health utility was identified from non-CML literature.
Method of preference elicitation for health state values	Choice-based method (e.g. TTO, SG, not rating scale)	✓	Values were elicited from a representative sample of 100 unaffected individuals in the UK using the time trade-off method and the EQ-5D instrument.
Source of preference data	Representative sample of the UK public	✓	
Discount rate	3.5% pa for costs and health effects	✓	

[3] Dasatinib and nilotinib for imatinib-resistant or –intolerant chronic myeloid leukaemia: A systematic review and economic evaluation. Peninsula Technology Assessment Group (PenTAG), Peninsula Medical School, Peninsula College of Medicine and Dentistry. NIHR HTA Programme project number 08/31/01.

Bristol-Myers Squibb Pharmaceuticals Limited

Uxbridge Business Park, Sanderson Road, Uxbridge, Middlesex UB8 1DH
Tel 01895 523000 Fax 01895 523010

TABLE 116 *Manufacturer submission for dasatinib (chronic phase): critical appraisal checklist*

Dimension of quality			Comments
	Structure		
S1	Statement of decision problem/objective	✓	Cost-effectiveness modelling of treatment with dasatinib v. treatment with high-dose imatinib or nilotinib in adults with chronic phase CML resistant or intolerant to previous therapy including imatinib. NICE are the primary decision maker.
S2	Statement of scope/perspective	✓	NHS perspective. Model inputs are consistent with the perspective. Scope of the model stated and justification given. Outcomes consistent with perspective and scope of the model.
S3	Rationale for structure	✓	Model structure has been described and is largely consistent with the progression of CML. The model uses the relationship between response to treatment and long-term survival to estimate long-term benefits. Sources of data used to develop the model structure are specified. Other model structures were considered.
S4	Structural assumptions	✓	Model assumptions were stated and justified.
S5	Strategies / comparators	✓	A clear definition of the comparators is provided and justified. Not all the comparators identified in the scope are evaluated – the analysis is limited to those believed to be most relevant. Differences in the baseline characteristics of individuals in the single arm trials of dasatinib, nilotinib and high-dose imatinib may render comparison invalid; these differences are not explored.
S6	Model type	✓	The model type is appropriate for this type of decision problem.
S7	Time horizon	✓	The time horizon is lifetime (100 years) which is appropriate to capture differences between treatment options. Treatment is continued until disease progression or until no longer tolerated. Due to the extensive data extrapolation needed to model a 100-year time horizon, a sensitivity analysis with a five-year time horizon is also included.

Bristol-Myers Squibb Pharmaceuticals Limited

Uxbridge Business Park, Sanderson Road, Uxbridge, Middlesex UB8 1DH
Tel 01895 523000 Fax 01895 523010

Dimension of quality			Comments
S8	Disease states / pathways	✓	The disease states reflect the biological pathway of the disease (chronic phase, accelerated phase, blast crisis and death) and the level of response on initiating treatment (initial best response and no initial response). Progression within chronic phase prior to progressing to accelerated phase does not appear to be captured in the model.
S9	Cycle length	✓	The cycle length is defined (monthly) and is justified in terms of the natural history of the disease and the frequency of follow-up of CML patients.
	Data		
D1	Data identification	✓	Data identification methods are described. The data for the main clinical parameters have been taken from single arm clinical trials. Data choices have been justified. The quality of the data has not been assessed. The use of healthcare resources in the treatment of CML and the management of serious adverse events was estimated by UK clinical experts; the methods of data collection are described. Health state utilities were elicited in a cross-sectional study; the methods are described.
D2	Pre-model data analysis	✓	Costs of healthcare resource use. Utility values for serious adverse events.
D2a	Baseline data	✓/×	All data are derived from single arm trials. Data for dasatinib is sourced from data on file; data for high-dose imatinib and nilotinib is sourced from the systematic literature review. The model does not use a baseline risk of disease progression or baseline treatment strategy directly. Levels of response to treatment are considered comparable to baseline risk as they determine the probability of disease progression for the rest of the analysis. Monthly rates of progression were calculated from the dasatinib clinical trials and applied in the model regardless of treatment. A half-cycle correction was used in the model; it is not clear whether this was applied to both costs and outcomes.
D2b	Treatment effects	✓/×	All data are derived from single arm trials. Imatinib-resistant and imatinib-intolerant populations were not considered separately. The model uses the relationship between attainment of a major cytogenetic response and overall survival seen with imatinib and assumes that the relationship will also be true for dasatinib and nilotinib. Survival at 24 months is used for dasatinib and nilotinib and survival at 3 months for high-dose imatinib. Methods of data extrapolation are not described, but disease progression is assumed to occur at a constant monthly rate. The model assumes that individuals move directly from chronic phase to accelerated phase which may not be an accurate reflection of clinical reality. The literature suggests that individuals may progress within chronic phase without meeting the criteria for accelerated phase. This is not captured in the model. Progression rates based on molecular response are assumed to be the same as complete cytogenetic response due to the lack of available data. Data used to derive treatment effects are likely to be subject to a large amount of uncertainty due to the range of sources from which they have been elicited and the length of extrapolation necessary to inform a 100 year model.
D2c	Quality of life weights (utilities)	✓	The methods of utility derivation are described. Utilities were commissioned in a cross sectional study of 100 representative unaffected individuals in the UK using the time trade off method and the EQ-5D instrument. The impacts of serious adverse events on health utility were taken from non-CML literature. The values used for chronic phase/response are similar to those collected in the IRIS trial of imatinib.
D3	Data incorporation	✓	Data incorporated into the model are referenced and generally well described. For the PSA, the input parameters and choice of distribution are described. All effectiveness data used in the model are derived from single arm trials, whilst this is described, the impact of the uncertainty associated with these methods is not explored.
D4	Assessment of uncertainty	✓/×	All types of uncertainty have been discussed, although only parameter uncertainty is explored to any extensive degree (through PSA)
D4a	Methodological	×	Other modelling methods were considered possible, however a Markov model was considered to be the most appropriate and alternative modelling approaches were not developed.
D4b	Structural	✓/×	This model is subject to a large amount of structural uncertainty that has not been discussed. Only the effect of differing time horizons was explored; the model has been run with two time horizons – 100 years (lifetime) and 5 years.
D4c	Heterogeneity	✓	No subgroup analyses were conducted, given the data available this is reasonable.
D4d	Parameter	✓	One-way and probabilistic sensitivity analyses have been performed.
	Consistency		
C1	Internal consistency	✓	The report states that the internal validity of the model was tested by using extreme values in the input parameters.

Dimension of quality			Comments
C2	External consistency	✓/×	The report states that results of the model have been compared with those of other published economic analyses and against trial data. However, it is also agreed that given the limited details available for previously published trials meaningful comparisons are difficult to perform. Few details of validation against trial data are provided.

Key: ✓: criteria met; ×: criteria not met; ✓/×: criteria partially met / unclear

TABLE 117 *Manufacturer submission for dasatinib (accelerated phase) – comparison with the NICE reference case*

NICE reference case requirement		Reviewer comment	
Decision problem	As per the scope developed by NICE (esp. technologies & patient group)	✓	Treatment with dasatinib of adults with CML resistant or intolerant to previous treatment including imatinib. Imatinib-resistant and imatinib-intolerant patients were not considered separately.
Comparator	Alternative therapies routinely used in the UK NHS	✓	imatinib (800mg/day) and nilotinib. Other comparators included in the scope (hydroxycarbamide, IFN and acute leukaemia chemotherapy) were not included in the analysis as not considered relevant.
Perspective on costs	NHS and PSS	✓	
Perspective on outcomes	All health effects on individuals	✓	
Type of economic evaluation	Cost-effectiveness analysis	✓	
Synthesis of evidence on outcomes	Based on a systematic review	✓	
Measure of health benefits	QALYs	✓	Life years gained were also measured.
Description of health states for QALY calculations	Use of a standardised and validated generic instrument		A cross sectional study was commissioned to calculate utility values. The impact of serious adverse events on health utility was identified from non-CML literature.
Method of preference elicitation for health state values	Choice-based method (e.g. TTO, SG, not rating scale)		Values were elicited from a representative sample of 100 unaffected individuals in the UK using the time trade-off method and the EQ-5D instrument.
Source of preference data	Representative sample of the UK public	✓	
Discount rate	3.5% pa for costs and health effects	✓	

Key: ✓: criteria met; ×: criteria not met; ✓/×: criteria partially met / unclear

TABLE 118 *Manufacturer submission for dasatinib (accelerated phase): critical appraisal checklist*

Dimension of quality			Comments
	Structure		
S1	Statement of decision problem/objective	✓	Cost-effectiveness modelling of treatment with dasatinib v. treatment with high-dose imatinib or nilotinib in adults with accelerated phase CML resistant or intolerant to previous therapy including imatinib. NICE are the primary decision maker.
S2	Statement of scope/perspective	✓	NHS perspective. Model inputs are consistent with the perspective. Scope of the model stated and justification given. Outcomes consistent with perspective and scope of the model.
S3	Rationale for structure	✓	Model structure has been described and is largely consistent with the progression of CML. The model uses the relationship between response to treatment and long-term survival to estimate long-term benefits. Sources of data used to develop the model structure are specified. Other model structures were considered.
S4	Structural assumptions	✓	Model assumptions were stated and justified.

Bristol-Myers Squibb Pharmaceuticals Limited

Uxbridge Business Park, Sanderson Road, Uxbridge, Middlesex UB8 1DH
Tel 01895 523000 Fax 01895 523010

Dimension of quality			Comments
S5	Strategies / comparators	✓	A clear definition of the comparators is provided and justified. Not all the comparators identified in the scope are evaluated – the analysis is limited to those believed to be most relevant. Differences in the baseline characteristics of individuals in the single arm trials of dasatinib, nilotinib and high-dose imatinib may render comparison invalid; these differences are not explored.
S6	Model type	✓	The model type is appropriate for this type of decision problem.
S7	Time horizon	✓	The model uses a lifetime time horizon (20 year) which may be unnecessarily long for those entering the model in accelerated phase. Treatment is continued until disease progression or until no longer tolerated. Due to the extensive data extrapolation needed to model a 20-year time horizon, a sensitivity analysis with a five-year time horizon is also included.
S8	Disease states / pathways	✓	The disease states reflect the biological pathway of the disease (accelerated phase, blast crisis and death) and the level of response on initiating treatment (initial best response and no initial response).
S9	Cycle length	✓	The cycle length is defined (monthly) and is justified in terms of the natural history of the disease and the frequency of follow-up of CML patients.
	Data		
D1	Data identification	✓	Data identification methods are described. Data choices have been justified. All data are derived from single arm trials. The quality of the data has not been assessed. The use of healthcare resources in the treatment of CML and the management of serious adverse events was estimated by UK clinical experts; the methods of data collection are described. Health state utilities were elicited in a cross-sectional study; the methods are described.
D2	Pre-model data analysis	✓	Costs of healthcare resource use. Utility values for serious adverse events.
D2a	Baseline data	×	All data are derived from single arm trials. Data for dasatinib is sourced from data on file, data for nilotinib are sourced from a conference abstract identified in the systematic literature review; there are no available data for high-dose imatinib in this population, data are therefore taken from a trial of standard dose imatinib in patients not displaying imatinib-resistance. The likelihood of treatment effects between these two populations being interchangeable is unclear and not discussed or explored. The model does not use a baseline risk of disease progression or baseline treatment strategy directly. Levels of response to treatment are considered comparable to baseline risk as they determine the probability of disease progression for the rest of the analysis. Monthly rates of progression were calculated from the dasatinib clinical trials and applied in the model regardless of treatment. A half-cycle correction was used in the model; it is not clear whether this was applied to both costs and outcomes.
D2b	Treatment effects	×	All data are derived from single arm trials. Imatinib-resistant and imatinib-intolerant populations were not considered separately. The model uses the relationship between attainment of a major cytogenetic response and overall survival seen with imatinib and assumes that the relationship will also be true for dasatinib and nilotinib. There is no available data on the treatment effects of high-dose imatinib in imatinib-resistant or intolerant patients in accelerated phase CML. The model therefore uses data from a trial of standard dose imatinib in first line treatment of accelerated phase CML. It is unlikely that these two scenarios are comparable. Survival at 24 months is used for dasatinib and nilotinib and survival at 3 months for high-dose imatinib. Methods of data extrapolation are not described, but disease progression is assumed to occur at a constant monthly rate. Progression rates based on molecular response were assumed to be the same as that for patients with complete cytogenetic response due to lack of available data. Data used to derive treatment effects are likely to be subject to a large amount of uncertainty due to the range of sources from which they have been elicited and the length of extrapolation necessary to inform a 20 year model.

Bristol-Myers Squibb Pharmaceuticals Limited

Uxbridge Business Park, Sanderson Road, Uxbridge, Middlesex UB8 1DH
Tel 01895 523000 Fax 01895 523010

Dimension of quality			Comments
D2c	Quality of life weights (utilities)	✓	The methods of utility derivation are described. Utilities were commissioned in a cross sectional study of 100 representative unaffected individuals in the UK using the time trade off method and the EQ-5D instrument. The impacts of serious adverse events on health utility were taken from non-CML literature. The values used for accelerated phase/ response are similar to those collected in the IRIS trial of imatinib.
D3	Data incorporation	✓	Data incorporated into the model are referenced and generally well described. For the PSA, the input parameters and choice of distribution are described. All effectiveness data used in the model are derived from single arm trials, whilst this is described, the impact of the uncertainty associated with these methods is not explored. Dose intensities of drugs have not been considered.
D4	Assessment of uncertainty	✓	All types of uncertainty have been discussed.
D4a	Methodological	×	Other modelling methods were considered possible, however a Markov model was considered to be the most appropriate and alternative modelling approaches were not developed.
D4b	Structural	✓/×	This model is subject to a large amount of structural uncertainty that has not been discussed. Only the effect of differing time horizons was explored; the model has been run with two time horizons – 20 years (lifetime) and 5 years.
D4c	Heterogeneity	✓	No subgroup analyses were conducted; given the data available this is reasonable.
D4d	Parameter	✓	One-way and probabilistic sensitivity analyses have been performed.
	Consistency		
C1	Internal consistency	✓	The report states that the internal validity of the model was tested by using extreme values in the input parameters.
C2	External consistency	✓/×	The report states that results of the model have been compared with those of other published economic analyses and against trial data. However, it is also agreed that given the limited details available for previously published trials meaningful comparisons are difficult to perform. Few details of validation against trial data are provided.

Key: ✓: criteria met; ×: criteria not met; ✓/×: criteria partially met / unclear

TABLE 119 Manufacturer submission for dasatinib (blast crisis) – comparison with the NICE reference case

NICE reference case requirement		Reviewer comment	
Decision problem	As per the scope developed by NICE (esp. technologies & patient group)	✓	Treatment with dasatinib of adults with CML resistant or intolerant to previous treatment including imatinib. Imatinib-resistant and imatinib-intolerant patients were not considered separately.
Comparator	Alternative therapies routinely used in the UK NHS	✓	imatinib (800mg/day) Other comparators included in the scope (hydroxycarbamide, IFN and acute leukaemia chemotherapy) were not included in the analysis as not considered relevant.
Perspective on costs	NHS and PSS	✓	
Perspective on outcomes	All health effects on individuals	✓	
Type of economic evaluation	Cost-effectiveness analysis	✓	
Synthesis of evidence on outcomes	Based on a systematic review	✓	
Measure of health benefits	QALYs	✓	Life years gained were also measured.
Description of health states for QALY calculations	Use of a standardised and validated generic instrument		A cross sectional study was commissioned to calculate utility values. The impact of serious adverse events on health utility was identified from non-CML literature.
Method of preference elicitation for health state values	Choice-based method (e.g. TTO, SG, not rating scale)		Values were elicited from a representative sample of 100 unaffected individuals in the UK using the time trade-off method and the EQ-5D instrument.
Source of preference data	Representative sample of the UK public	✓	
Discount rate	3.5% pa for costs and health effects	✓	

Key: ✓: criteria met; ×: criteria not met; ✓/×: criteria partially met / unclear

TABLE 120 Manufacturer submission for dasatinib (blast crisis): critical appraisal checklist

Dimension of quality			Comments
	Structure		
S1	Statement of decision problem/objective	✓	Cost-effectiveness modelling of treatment with dasatinib v. treatment with high-dose imatinib in adults with blast crisis CML resistant or intolerant to previous therapy including imatinib. NICE are the primary decision maker.
S2	Statement of scope/perspective	✓	NHS perspective. Model inputs are consistent with the perspective. Scope of the model stated and justification given. Outcomes consistent with perspective and scope of the model.
S3	Rationale for structure	✓	Model structure has been described and is largely consistent with the progression of CML. The model uses the relationship between response to treatment and long-term survival to estimate long-term benefits. Sources of data used to develop the model structure are specified. Other model structures were considered.
S4	Structural assumptions	✓	Model assumptions were stated and justified.
S5	Strategies / comparators	✓	A clear definition of the comparators is provided and justified. Not all the comparators identified in the scope are evaluated – the analysis is limited to those believed to be most relevant. Differences in the baseline characteristics of individuals in the single arm trials of dasatinib and nilotinib may render comparison invalid, these differences are not explored.
S6	Model type	✓	The model type is appropriate for this type of decision problem.

Bristol-Myers Squibb Pharmaceuticals Limited

Uxbridge Business Park, Sanderson Road, Uxbridge, Middlesex UB8 1DH
Tel 01895 523000 Fax 01895 523010

Dimension of quality			Comments
S7	Time horizon	✓	The time horizon used is lifetime (20 years) which may be unnecessarily long for people entering the model in blast crisis. Treatment is continued until disease progression or until no longer tolerated. Due to the extensive data extrapolation needed to model a 20-year time horizon, a sensitivity analysis with a five-year time horizon is also included.
S8	Disease states / pathways	✓	The disease states reflect the biological pathway of the disease (blast crisis and death) and the level of response on initiating treatment (initial best response and no initial response).
S9	Cycle length	✓	The cycle length is defined (monthly) and is justified in terms of the natural history of the disease and the frequency of follow-up of CML patients.
	Data		
D1	Data identification	✓	Data identification methods are described. Data choices have been justified. All data are derived from single arm trials. The quality of the data has not been assessed. The use of healthcare resources in the treatment of CML and the management of serious adverse events was estimated by UK clinical experts; the methods of data collection are described. Health state utilities were elicited in a cross-sectional study; the methods are described.
D2	Pre-model data analysis	✓	Costs of healthcare resource use. Utility values for serious adverse events.
D2a	Baseline data	×	All data are derived from single arm trials. Data for dasatinib is sourced from data on file. There are no available data for high-dose imatinib in this population; data are therefore taken from a trial of standard dose imatinib in patients not displaying imatinib-resistance. The likelihood of treatment effects between these two populations being interchangeable is unclear and is not discussed or explored. The model does not use a baseline risk of disease progression or baseline treatment strategy directly. Levels of response to treatment are considered comparable to baseline risk as they determine the probability of disease progression for the rest of the analysis. Monthly rates of progression were calculated from the dasatinib clinical trials and applied in the model regardless of treatment. A half-cycle correction was used in the model; it is not clear whether this was applied to both costs and outcomes.
D2b	Treatment effects	×	All data are derived from single arm trials. Imatinib-resistant and imatinib-intolerant populations were not considered separately. The model uses the relationship between attainment of a major cytogenetic response and overall survival seen with imatinib and assumes that the relationship will also be true for dasatinib and nilotinib. There is no available data on the treatment effects of high-dose imatinib in imatinib-resistant or intolerant patients in blast crisis CML. The model therefore uses data from a trial of standard dose imatinib in first line treatment of accelerated phase CML. It is unlikely that these two scenarios are comparable. Survival at 24 months is used for dasatinib and nilotinib and survival at 3 months for high-dose imatinib. Methods of data extrapolation are not described, but disease progression is assumed to occur at a constant monthly rate. Progression rates based on molecular response were assumed to be the same as that for patients with complete cytogenetic response due to lack of available data. Data used to derive treatment effects are likely to be subject to a large amount of uncertainty due to the range of sources from which they have been elicited and the length of extrapolation necessary to inform a 20 year model.
D2c	Quality of life weights (utilities)	✓	The methods of utility derivation are described. Utilities were commissioned in a cross sectional study of 100 representative unaffected individuals in the UK using the time trade off method and the EQ-5D instrument. The impacts of serious adverse events on health utility were taken from non-CML literature. The values used for accelerated phase/ response are similar to those collected in the IRIS trial of imatinib.
D3	Data incorporation	✓	Data incorporated into the model are referenced and generally well described. For the PSA, the input parameters and choice of distribution are described. All effectiveness data used in the model are derived from single arm trials, whilst this is described, the impact of the uncertainty associated with these methods is not explored.

Bristol-Myers Squibb Pharmaceuticals Limited

Uxbridge Business Park, Sanderson Road, Uxbridge, Middlesex UB8 1DH
Tel 01895 523000 Fax 01895 523010

Dimension of quality			Comments
D4	Assessment of uncertainty	✓	All types of uncertainty have been discussed.
D4a	Methodological	×	Other modelling methods were considered possible, however a Markov model was considered to be the most appropriate and alternative modelling approaches were not developed.
D4b	Structural	✓/×	This model is subject to a large amount of structural uncertainty that has not been discussed. Only the effect of differing time horizons was explored; the model has been run with two time horizons – 20 years (lifetime) and 5 years.
D4c	Heterogeneity	✓	No subgroup analyses were conducted; given the data available this is reasonable.
D4d	Parameter	✓	One-way and probabilistic sensitivity analyses have been performed.
	Consistency		
C1	Internal consistency	✓	The report states that the internal validity of the model was tested by using extreme values in the input parameters.
C2	External consistency	✓/×	The report states that results of the model have been compared with those of other published economic analyses and against trial data. However, it is also agreed that given the limited details available for previously published trials meaningful comparisons are difficult to perform. Few details of validation against trial data are provided.

Key: ✓: criteria met; ×: criteria not met; ✓/×: criteria partially met / unclear

Bristol-Myers Squibb Pharmaceuticals Limited

Uxbridge Business Park, Sanderson Road, Uxbridge, Middlesex UB8 1DH
Tel 01895 523000 Fax 01895 523010

Appendix 4

Summary of Incremental Cost Effectiveness Ratios for SHTAC Model and BMS submitted models

SUMMARY: ALL RESULTS IN THE IMATINIB RESISTANT GROUP

Drug	Comparator	Model	Disease stage	Treatment Horizon	ICER (per QALY gained)	Other Comments
Dasatinib	High dose imatinib	BMS original	CP	n/a	Dominated	Dasatinib provides greater benefit at less cost
Dasatinib	High dose imatinib	SHTAC	CP	6.5	Dominated	Dasatinib provides greater benefit at less cost
Dasatinib	High dose imatinib	SHTAC	CP	10	Dominated	Dasatinib provides greater benefit at less cost
Nilotinib	Hydroxyurea	SHTAC original	CP	n/a	£26,434	
Dasatinib	Hydroxyurea	SHTAC	CP	6.5	£36,007	
Dasatinib	Hydroxyurea	SHTAC	CP	10	£43,816	Base case ICER used by the Committee
Dasatinib	Hydroxyurea	BMS revised	CP	n/a	£27,932	
Dasatinib	interferon alfa	BMS original	CP	n/a	£38,883	
Dasatinib	Nilotinib	BMS original	CP	n/a	Dominated	Dasatinib provides greater benefit at less cost
Dasatinib	Nilotinib	SHTAC original	CP	n/a	£50,016	
Dasatinib	Nilotinib	SHTAC	CP	6.5	Dominated	Dasatinib provides greater benefit at less cost
Dasatinib	Nilotinib	SHTAC	CP	10	Dominated	Dasatinib provides greater benefit at less cost

Bristol-Myers Squibb Pharmaceuticals Limited

Uxbridge Business Park, Sanderson Road. Uxbridge, Middlesex UB8 1DH
Tel 01895 523000 Fax 01895 523010

Drug	Comparator	Model	Disease stage	Treatment Horizon	ICER (per QALY gained)	Other Comments
Dasatinib	"No treatment"	BMS original	BP	n/a	£25,531	Note it would appear that PenTAG performed this analysis using the BMS model
Dasatinib	High dose imatinib	BMS original	AP/BP	n/a	£36,594	
Dasatinib	High dose imatinib	BMS original	BP	n/a	Dominated	Dasatinib provides greater benefit at less cost
Dasatinib	High dose nilotinib	BMS original	AP/BP	n/a	£32,405	
Dasatinib	SCT	BMS original	AP/BP	n/a	£231,650	Dasatinib provides less benefit and is less costly
Dasatinib	SCT	BMS original	BP	n/a	£54,093	Dasatinib provides less benefit and is less costly

Key: CP = Chronic phase, AP = Accelerated phase, BP = Blast crisis phase