All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

AWMSG ADVICE PARTIALLY SUPERSEDED BY NICE GUIDANCE (TA241)

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Final Appraisal Report

Dasatinib (Sprycel®) for the treatment of Lymphoid blast CML and PH+ ALL

Bristol-Myers Squibb Pharmaceuticals Ltd

Advice No: 1407 – December 2007

Recommendation of AWMSG

Dasatinib (Sprycel®▼) is not recommended for use within NHS Wales for the treatment of adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) and lymphoid blast chronic myeloid leukaemia (LB-CML) with resistance or intolerance to prior therapy.

This assessment report is based on evidence submitted by Bristol-Myers Squibb Pharmaceuticals Ltd on 9th July 2007

This report should be cited as:

1.0 RECOMMENDATION OF AWMSG:

Date: 11th December 2007

The recommendation of AWMSG is:

Dasatinib (Sprycel®) is not recommended for use within NHS Wales for the treatment of adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) and lymphoid blast chronic myeloid leukaemia (LB-CML) with resistance or intolerance to prior therapy.

Key factors influencing the recommendation:

Based on the available evidence, the AWMSG consider that dasatinib does not represent a cost-effective use of healthcare resources for the lymphoid blast phase of CML and Ph+ ALL. The economic model submitted relies on a number of substantial assumptions e.g. utility values, disease progression, which are inadequately justified. As a result, an economic case was not demonstrated in patients who are resistant to usual doses of imatinib.

For patients in the blast phase of CML where imatinib is failing, the AWMSG suggest that these patients should be considered for entry into clinical trials to clarify the position of further therapy.

There are no published randomised controlled trials directly comparing dasatinib with current therapeutic treatment options for patients with Ph+ ALL and LB-CML.

2.0 PRODUCT DETAILS:

2.1 Licensed indication:

Dasatinib (Sprycel®) is licensed for the treatment of adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) and lymphoid blast chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy[1].

2.2 Dosing:

The recommended dosage is 70 mg twice daily, administered orally in the morning and in the evening, with or without a meal. In clinical trials of blast phase CML and Ph+ ALL patients, dose escalation up to 100 mg twice daily was allowed in those who did not achieve a haematologic or cytogenetic response[1].

2.3 Market authorisation date: 20th November 2006[2]

2.4 UK Launch date: November 2006[2]

3.0 DECISION CONTEXT

This appraisal focuses on dasatinib treatment for lymphoid blast CML and Ph+ ALL. The additional licensed indication for chronic, accelerated and blast phase CML is the subject of AWMSG appraisal number 1307.

CML and Ph+ ALL are rare haematopoietic stem cell disorders.

Lymphoid blast CML (LB-CML)

Ninety-five percent of people with CML have a chromosomal abnormality caused by a reciprocal translocation of genetic material between chromosomes 22 and 9: the 'Philadelphia chromosome'. Consequently a BCR-ABL fusion gene is produced which codes for protein that has higher than usual tyrosine phosphokinase activity. This results in bone marrow production of an excessive number of abnormal stem cells which eventually suppress the production of normal white blood cells[2]. CML accounts for about 20 percent of newly diagnosed cases of leukaemia in adults. The course of the disease is triphasic: a chronic phase lasting three to six years is followed by transformation to accelerated and then blast phases of short duration[3]. The majority of CML patients at diagnosis are in the chronic phase, with the remainder of patients diagnosed in the accelerated phase or blast crisis (BC). The BC may be myeloid, lymphoid, or undifferentiated/mixed, with myeloid blast crisis (MBC) being approximately twice as common as lymphoid (LBC). The prognosis is poor; overall survival from the onset of BC is approximately 3 to 6 months.

In 2003 NICE recommended imatinib as first-line treatment for people with Philadelphia-chromosome positive CML in the chronic phase and as an option for patients who present in the accelerated or blast phase or progress from chronic to advanced disease and who have not previously received imatinib. The guidance recommends the continued use of imatinib where treatment has failed to stop the advancement of the disease in the context of further clinical study only[4]. NICE advice is due to be reviewed in 2009 pending the results of ongoing studies[5].

Allogeneic stem cell transplantation (SCT) induces durable remission in less than 10% of patients with CML in BC and imatinib yields sustained complete haematological responses (CHRs) in less than 15%. Failure to respond to imatinib is particularly common during BC compared with earlier stages of the disease[6]. The British Committee for Standards in Haematology (BCSH) recommend the use of second generation tyrosine kinase inhibitors (such as dasatinib) in patients who have progressed to blast phase CML whilst taking imatinib. Allogeneic SCT should also be considered if a suitable donor can be identified. For patients presenting in advanced disease who initially respond to imatinib, duration of response may be short and continuing treatment immediately after the initial response should involve use of conventional chemotherapy with or without SCT[7]. The BCSH guidelines also suggest that SCT should be considered in patients in BC–CML already on imatinib treatment[7].

ALL

ALL results from the uncontrolled proliferation and expansion of immature lymphoid cells which eventually affects the production of normal blood cells. At least 25% of people with ALL have the Philadelphia chromosomal abnormality as described above; these cases are called Ph+ ALL[2].

The prognosis of adult patients with Ph+ ALL treated only with chemotherapy is poor, with a less than 10% probability of long-term survival[8]. SCT is considered to be the treatment of choice in adult Ph+ ALL, with 27-65% long-term survival being reported for patients undergoing SCT whilst in first complete remission. Although imatinib can induce responses in a subset of these patients, resistance to the drug develops rapidly.

Dasatinib is a protein kinase inhibitor which inhibits BCR-ABL kinase and has been demonstrated as active against 20 out of 21 imatinib BCR-ABL mutations in vitro[2]. Dasatinib binds to the BCR-ABL kinase in both active and inactive conformations which is suggested to give a reduced propensity for acquired drug resistance on continued exposure[9]. Imatinib only binds to the inactive conformation[2].

4.0 EXECUTIVE SUMMARY:

4.1 Review of the evidence on clinical effectiveness

The company have based their submission on one Phase II trial which is non comparative. There is evidence of response to dasatinib despite prior intolerance or resistance to imatinib in patients with both Ph+ ALL and LB-CML.

A major haematological response (MaHR) was seen in 35% of LB-CML and 41% of Ph+ ALL patients, with a median duration of 4.9 and 7.6 months respectively.

Over half of all patients achieved a major cytogenetic response (MCyR), with an improved response rate in Ph+ ALL patients who had undergone prior SCT. It is important to note that the long term follow up data at 18.5 months has only been presented at conference.

The most frequently reported non-haematological adverse events (AEs) from the clinical trial programme (including CA180015) were fluid retention (including pleural effusion), diarrhoea, skin rash, headache, haemorrhage, fatigue, nausea and dyspnoea. The majority of adverse events were considered to be drug-related. The European Public Assessment Report (EPAR) for dasatinib comments that most of the identified risks were manageable, and adds that long-term safety data on treatment with dasatinib had important missing information.

4.2 Review of the evidence on cost-effectiveness

The economic model compares dasatinib 70mg twice daily with high dose imatinib (400mg twice daily) in patients with lymphoid blast chronic myeloid leukaemia (LB-CML) and Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL) that are resistant to usual dose imatinib. The use of dasatinib in patients intolerant to usual dose imatinib has not been considered. Due to a lack of data, the model is essentially based on that used for blast phase CML and relies upon a number of assumptions related to disease progression, the utility values associated with response to treatment, and the impact and costs of adverse events. Dasatinib treatment is associated with high incremental costs per QALY that exceed conventional thresholds of cost-effectiveness under the most optimistic parameter values tested.

WMP is mindful of the ultra-orphan drug status of dasatinib. However, the economic case for dasatinib is not robust as many of the assumptions made in the analysis are unsupported by evidence. The resulting uncertainty around the cost-effectiveness of dasatinib in patients with LB-CML or Ph+ ALL, who are resistant to usual doses of imatinib, indicates that the economic case has not been demonstrated.

5.0 LIMITATIONS OF DECISION CONTEXT:

- There are no published randomised controlled trials directly comparing dasatinib with current therapeutic treatment options for patients with Ph+ ALL and LB-CML.
- No trials have been undertaken in patients with hepatic or renal impairment, or uncontrolled or significant cardiovascular disease.
- Long-term follow up data has only been presented at conference and not published in peer reviewed journals.

6.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

6.1 Clinical efficacy:

Five Phase II clinical studies comprise the **S**RC/ABL **T**yrosine kinase inhibition **A**ctivity **R**esearch **T**rials of BMS-354825 or 'START' programme. One of these, START-L (CA180015), was a single-arm study which focuses on patients with Ph+ALL and LB-CML and is the basis of the company submission[2].

Haematological and cytogenetic measures are the commonly used endpoints in studies of leukaemia treatment. Haematological outcomes include relative absence of leukaemic cells and normalisation of blood cell counts. Cytogenetic measures are graded on the

percentage of Ph+ cells in the bone marrow. Appendix 1, table one, details the cytogenetic response criteria for the START programme[2].

6.1.1 START- L (CA180015)[9,10,11,12]

This was an open-label multicentre, single-arm study in patients with LB-CML or Ph+ ALL, resistant or intolerant to imatinib. Of the 48 patients with LB-CML, 88% (n=42) were imatinib resistant, 52%(n=25) had received imatinib ≥600mg/day and 23% (n=11) treatment for more than 12months [2,12]. Of the 46 patients with Ph+ ALL, 95.6% (n=44) were imatinib resistant, 46% (n=21)had received ≥ 600mg/day and 52% treatment for more than 12months[2,12]. Patients with LB-CML had a mean age of 47 years (range 19–72) and patients with Ph+ ALL a mean age of 48 years (range 15-85)[2].

Patients received dasatinib 70mg twice daily. Hydroxyurea and anagrelide were permitted for a maximum of two weeks. The primary efficacy endpoints were overall haematological response (OHR) and major haematological response (MaHR). The latter consisted of complete haematological response (CHR) and no evidence of leukaemia (NEL). Secondary endpoints were durability and time to MaHR and OHR as well as the rate of major cytogenetic response (MCyR). The dose could be increased up to 100mg twice daily for inadequate response[2].

Interim results (follow-up 8 months) have been published[9] and presented at the American Society of Haematology (ASH) conference 2006 for patients with LB-CML[10] For patients with Ph+ ALL, interim results (8 months) have been published[11] and the follow up data presented at the European Haematology Association (EHA) 2007 conference[12].The follow up data presented at conference is included as appendices within the Form B submission and is also included within this appraisal for completeness. It must be noted that this information has not been published in a peer reviewed publication.

Table one. Primary Efficacy Results from START- L (CA180015)

End Points: Haematological Response Rate	**Follow-up 8 months**		**Follow-up 18.5 months (median 2.96)**	
	LB-CML[9] (n=42)	**Ph+ ALL[11] (n=36)**	**LB-CML [10](n=48)**	**Ph+ ALL[12] (n=46)**
OHR	36%	47%	39%	50%
MaHR	31%	42%	35%	41%
CHR	26%	31%	29%	33%
NEL	5%	11%	6%	9%

Follow-up ranged from <1 to 18.5 months.
Of the17 LB-CML patients who achieved a MaHR, 9 progressed[2].
Of the15 Ph+ ALL patients who achieved a MaHR, 5 progressed[2].

Table two. Secondary Efficacy Results from START- L (CA180015)

End Points: Cytogenetic response rate	Follow-up 8 months		Follow-up 18.5 months (median 2.96)	
	LB-CML[9] (n=42)	Ph+ ALL[11] (n=36)	LB-CML[10] (n=48)	Ph+ ALL[12] (n=46)
MCyR	50%	58%	52%	57%
CCyR	43%	58%	46%	54%

MCyR = major cytogenetic response CCyR = complete cytogenetic response

In 37% (n=17) patients with PH+ ALL who had undergone prior SCT, the MaHR and MCyR rates were higher than average, at 47% and 76% respectively. MCyRs occurred quickly (median 29 days) and were durable (median 6.9 months).
15% (n=7) of LB-CML patients underwent SCT following dasatinib treatment.

Table three. Median duration of response from START- L (CA180015)

Endpoints: Response	Median duration of response	
	LB-CML[10]	Ph+ ALL[12]
MaHR	4.9 months	7.6 months
PFS	3.0 months	3.7 months
OS	5.3 months	8.0 months

PFS = Progression-free survival OS = Overall survival

Points to note

- Some of the data submitted within Form B has only been presented at the ASH 2006 and EHA 2007 conferences and not peer reviewed, but has been included in this appraisal for completeness. The data submitted to the EMEA was that of a published interim analysis[13].
- Subjects were excluded if they had uncontrolled or significant cardiovascular disease or inadequate hepatic or renal function[2].
- The median age for adults with Ph+ ALL is older than 60 years, but relatively few of these patients seem to have been enrolled in this trial. Presence of co-existing disease within this population presents a considerable challenge for successful treatment outcomes[14].
- Although one of the inclusion criteria was that of prior imatinib exposure, this did not need to be their most recent treatment[13].
- Patients were not considered intolerant of imatinib if they were intolerant of doses greater than 400mg/day[13].
- 59% (n=27) of Ph+ ALL patients received dose escalations to 100mg twice daily, whilst dose reductions were needed by 30% (n=14)[12].
- At the time of the interim analysis, 24/36 (67%) of Ph+ ALL patients, all of whom were imatinib resistant, had discontinued dasatinib treatment. The median duration of therapy was 3.2 months range (0.2 - 8.1months)[13].
- The Eastern Co-operative Oncology Group (ECOG) performance status of all study participants was ≤ 2[12].

6.2 Safety:

The most frequently reported adverse events during clinical trials with dasatinib include gastrointestinal disorders, rash, fluid retention, fatigue, asthenia, pyrexia and dyspnoea. Severe cases of fluid retention occurred in 7% of patients. Severe gastrointestinal (GI) haemorrhage occurred in 5% of patients and generally required treatment interruptions and transfusions[13]. Approximately 14% of patients within the dasatinib programme experienced a pleural effusion and 40-50% of patients had raised liver enzymes at some stage during the study[13]. The company submission refers to the presentations at EHA 2007 and ASH 2006 congresses for more up-to-date safety data. Dasatinib may be associated with decreased platelet count more commonly than imatinib[2].

Adverse events (AEs) leading to discontinuation occurred in 34% (n=32) of patients with LB-CML or Ph+ ALL, and most of these were Grade 3 to 4; most commonly disease worsening and blast crisis[2]. A total of 35 (37%) deaths were reported in LB–CML and Ph+ ALL subjects. 16 (18%) were due to disease progression, 11 (13%) due to infection, 3 (3%) due to fatal bleeding and 6 (7%) reported as other. The “other” reasons included pleural effusion, constrictive pericarditis and respiratory failure. GI disorder AEs were the largest percentage of drug-related non-haematological AEs (7%) within this trial and all were considered severe (grade 3 to 4); GI haemorrhage constituted the greatest proportion (2%) of these events[13].

Patients with symptoms of pleural effusion e.g. dyspnoea, require additional evaluation and potentially thoracentesis and oxygen therapy with subsequent interruption to therapy and possible dose reduction[2].The majority of LB-CML and Ph+ ALL patients with grade 0 counts developed grade 3 to 4 neutropenia (67%) and thrombocytopenia (33%). 50% of patients with LB-CML and Ph+ ALL entered the study with a baseline toxicity grade 3 to 4. Overall toxicity to dasatinib is rated to be manageable [13].

The EPAR for dasatinib comments that most of the identified risks were manageable, but adds that long-term safety data on the treatment with dasatinib is important missing information[13].One out of 71 deaths within studies CA180006 and CA180015 is considered to be caused by the study drug. The EMEA state that this may be underestimated given the potential toxicity of dasatinib (e.g. neutropenia, thrombocytopenia)[13]. The EMEA have accepted a risk management plan, which includes risk minimisation activities, with regard to the potential safety concerns highlighted[13].Study CA180033 is currently underway in 400 patients and is intended to assess the efficacy and safety of dasatinib across all phases of CML and Ph+ ALL[2].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES:

7.1 Comparator medications:

CML is potentially curable with SCT, but fewer than 30 percent of patients have suitably matched donors and the procedure carries major risks. Treatment with interferon alfa can induce a complete cytogenetic response in 5 to 20 percent of patients and result in a longer survival than that achievable with chemotherapy, but it is associated with serious toxic effects. Patients in whom interferon therapy fails are usually treated with hydroxyurea, busulfan, or investigational agents. The rate of response decreases rapidly

as the time from the initial diagnosis to the initiation of second-line therapy increases, particularly when such therapy is started in the late chronic phase, defined as more than12 months after the initial diagnosis[3].
The prognosis of adult patients with Ph+ ALL treated only with chemotherapy is poor, with a less than 10% probability of long-term survival[2]. SCT is considered to be the treatment of choice in adult Ph+ ALL. Although imatinib can induce responses in a subset of these patients, resistance to the drug develops rapidly.
A number of therapies are under investigation; the one closest to licence is nilotinib, a tyrosine kinase inhibitor that has also been shown to be effective in imatinib-resistant CML and, like dasatinib, is active against imatinib-resistant mutations with the exception of T315I. Agents active against T315I are in development.

7.2 Comparative effectiveness:

There are no published comparative trial data on treatment of patients with LB–CML or Ph+ ALL.

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE:

8.1 Overview of the key economic issues for the AWMSG to consider

The key economic issue for the AWMSG to consider is whether the additional benefits offered by dasatinib over the relevant comparator justify the associated costs.

8.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have not identified any published economic studies of the use of dasatinib in the management of patients with Ph+ ALL or LB-CML with resistance or intolerance to prior therapy.

8.3 Review of company submission on cost-effectiveness

8.3.1 Summary of the evidence

The company submission[2] describes a Markov model, which is essentially based on the modelled myeloid blast phase CML presented in a separate company submission of dasatinib in the treatment of CML[15]. This approach assumes that the features of LB-CML and Ph+ ALL are similar to myeloid blast CML in terms of utilities, etc., which is a major limitation of the model. The company submission acknowledges that a number of assumptions have been made in the cost-effectiveness analysis and duly states that: "…results presented…have to be treated with caution due to the paucity of data used"[2].

The model estimates the cost-utility of dasatinib in adult patients with LB-CML and Ph+ ALL that is resistant to imatinib used at daily doses of less than 600mg. The licensed indication for dasatinib includes patients who are intolerant to imatinib[1]; however, this patient group is not considered in the economic analysis[2]. Following initial treatment, patients with LB-CML and Ph+ ALL enter one of three states: initial best response, no initial response or death. From these three states, patients either remain in their initial LB-CML/Ph+ ALL phase or die. Patients are initially treated with either dasatinib 70mg twice daily or imatinib 400mg twice daily until progression.

The initial probabilities of response to treatment for dasatinib are derived from study CA180-015[2]. It is not immediately clear where some of the figures used to estimate the probabilities of initial best response have been derived from, as the figures used in the model appear to have some discrepancies. In addition, these two studies appear to have evaluated the efficacy of 400mg and 600mg initial daily doses of imatinib, rather than 400mg twice daily (although a minority of patients did receive doses of 400mg twice daily at least once during the studies). The reliability of these probabilities of initial treatment response is therefore unclear.

The probabilities of progressing to the next phase of CML or death have been derived from published studies of imatinib. It is assumed that the prognosis of patients who have a given response to initial treatment is the same irrespective of the initial treatment they receive. This is a limitation of the model, as it feasible that the prognosis of patients resistant to usual dose imatinib could be different when treated with high dose imatinib versus dasatinib.

A study was commissioned to calculate utility weights for the purpose of this analysis[2]. These utility values were solicited from a group of one hundred unaffected individuals in the UK. Utility weights for a state called 'adverse events' were also elicited in this study but details are lacking and no utility values associated with any adverse events appear to have been included in the base case analysis. There appear to be significant differences in the probabilities of some adverse events used in the model and those reported in other sources.

The model considers direct costs from the perspective of NHS Wales[2]. The costs of serious adverse events were included in the analysis, but adverse events and their associated costs were assumed only to occur in the first three months of treatment. Resource use (excluding dasatinib and imatinib drug treatment costs) has been estimated on the basis of the opinion of two haemotologists, one from Wales and one from Scotland.

A series of one-way sensitivity analyses were carried out to determine the impact of various individual parameters on the model outputs for treatment started in the chronic, accelerated and blast phases of CML. The probabilities of treatment response and progression, the probabilities of and costs of adverse events, and the daily dose of dasatinib were not explored. Separate probabilistic sensitivity analyses (PSA) have not been conducted for LB-CML and Ph+ ALL.

8.3.2 Summary of the key findings

The incremental costs per QALY gained for treatment with dasatinib 70mg twice daily compared with imatinib 400mg twice daily are presented in the following table[2]:

	LB-CML	**Ph+ ALL**
Incremental costs	£86,559	£4,971
Incremental QALYs	1.31	0.08
ICER	**£66,158**	**£61,533**
Life time horizon, all values discounted at 3.5%		

For LB-CML, none of the one-way sensitivity analyses that were conducted reduced the ICER to less than £49,950 per QALY gained. The model appeared most sensitive to the assumptions on utilities associated with response to treatment (varying utilities by ±20% resulted in the ICER

ranging from £54,632 to £83,848 per QALY gained). The model was also sensitive to the assumptions of disutility associated with adverse effects, which is relevant given the uncertainty in the assumptions used. Reducing the daily dose of imatinib from 800mg to 600mg increased the ICER to £70,251 per QALY gained[2].

For Ph+ ALL, none of the one-way sensitivity analyses that were conducted reduced the ICER to less than £51,230 per QALY gained. The model appeared to be very sensitive to the assumptions of the utilities associated with response to treatment (varying utilities by ±20% resulted in the ICER ranging from £51,231 to £77,020 per QALY gained) and disutility associated with adverse events. Reducing the daily dose of imatinib from 800mg to 600mg increased the ICER to £81,560 per QALY gained[2].

8.4 Review of evidence on budget impact:

8.4.1 Summary of the evidence

The perspective adopted by the budget impact analysis is that of NHS Wales (though only drug acquisition costs are considered), with a five-year time horizon starting in 2008[2]. Incidence rates are not used in the model, on the basis that the disease prevalence captures the flow of new patients and mortality[2].

The company submission states that the total number of patients suitable for treatment with dasatinib in 2008 will be 17 (13 Ph+ ALL patients + 4 LB-CML patients). The company submission then states that a maximum of 23 patients in 2008 and 24 patients in each year 2009–12 will receive dasatinib. This is reported to be based on a number of assumptions around the treatment of patients with myeloid blast CML and data from surveys, which are not verifiable. The estimates of the number of patients to be treated in 2008 appear to be inconsistent with the figures quoted previously in the company submission. Therefore, the number of patients quoted as likely to be eligible for treatment with dasatinib must be treated with caution.

The budget impact model assumes that patients newly diagnosed with CML would be considered for HSCT, then imatinib, and then dasatinib[2]. It assumes 100% uptake in patients who are resistant to or intolerant of imatinib in the base-case and a slower rate of uptake is explored in another scenario.

The company submission provides figures for the doses of imatinib used based on a physician survey. Well managed patients receive 600mg once daily. Resistant patients with blast CML are reported to receive higher doses, on average 721mg and this dose has been assumed for patients with LB-CML and Ph+ ALL. Intolerant patients in any CML phase are reported to receive 300mg once daily. This is data on file and cannot be verified. Dasatinib recipients are assumed to receive 70mg twice daily in all phases. The cost of imatinib treatment, in the absence of dasatinib as an alternative, has been calculated by applying the cost per mg of imatinib to the average daily doses of imatinib used by resistant, intolerant and well managed patients. The cost of dasatinib if used in all imatinib resistant and intolerant patients is estimated by applying the cost of dasatinib 70mg twice daily to each of these patients.

8.4.2 Summary of the key findings

Assuming 100% uptake, the cost of using dasatinib instead of imatinib is estimated to save approximately £28,800 in 2008 and £29,300 in each of years 2009–12 (i.e. dasatinib treatment is less expensive than imatinib treatment).

A scenario of a slower rate of uptake has also been modelled. If uptake is 50% in 2008, 75% in 2009 and 100% in subsequent years, the cost savings with the use of dasatinib instead of imatinib would be £14,400 in 2008, £22,000 in 2009 and £29,300 in 2010–12.

These figures must be viewed with caution given the range of assumptions used, inconsistencies in calculation of patient numbers, etc. No sensitivity analysis has been conducted.

9.0 ADDITIONAL INFORMATION:

9.1 Guidance and audit requirements:

- Dasatinib would not be suitable for a shared-care agreement. Treatment initiation, monitoring and supervision should be retained under Specialist care.
- BCSH recommend the use of second generation tyrosine kinase inhibitors (such as dasatinib) or allogenic SCT for patients with suitable donors for patients who have progressed to blast phase CML whilst taking imatinib. For patients initially responding to imatinib in blast phase transformation, treatment should include interferon alfa or hydroxycarbamide with or without SCT[7].

9.2 Previous NICE advice

NICE issued the following guidance in October 2003: “Imatinib is recommended as first-line treatment for people with PH+ CML in the chronic phase. Imatinib is recommended as an option for the treatment of people with PH+ CML who initially present in the accelerated phase or with blast crisis”.

Additionally, imatinib is recommended as an option for people who present in the chronic phase and then progress to the accelerated phase or blast crisis if they have not received imatinib previously. There is currently no evidence on clinical and cost effectiveness on which to base guidance on the continued use of imatinib that has been initiated in the chronic phase of CML but has failed to stop disease progression to either the accelerated phase or blast crisis [4].

9.3 Ongoing studies[2]

- CA180033 – a phase II single arm study in 400 patients across all phases of CML.
- GIMEMA Protocol LAL1205 – phase II study in 48 Ph+ ALL patients.
- CA180035 – a phase II study of once daily and twice daily dosing in 611 patients across all phases of CML and Ph+ ALL.
- CA180018 – paediatric study.

9.4 Medical Expert

Medical expert opinion was sought prior to the meeting and provided a summary to AWMSG members.

First line treatment for LB-CML and Ph+ ALL in NHS Wales is chemotherapy plus imatinib followed by BMT if possible. There is a need for an alternative protein kinase inhibitor for patients intolerant or resistant to imatinib. There is limited experience in this indication. It would be useful to develop a group to ensure even-handedness in its usage throughout Wales and define the indications a little more clearly.

There is a poor record of treatment response once the disease enters the blastic phase. Any new treatments here would be welcomed.

An estimate of Ph positive ALL in Wales for both children and adults is around 8-10 cases per year.

9.5 Patient Interest Group

A patient interest group submission by Leukaemia Care was provided to AWMSG members.

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Appendix 1. Additional clinical information

Table one: Cytogenetic Response Criteria for START trials[2]:

Response	Philadelphia positive (PH+) cells in metaphases in bone marrow sample
Complete Cytogenetic Response (CCyR)	0%
Partial Cytogenetic Response (PCyR)	1% to 35%
Minor Cytogenetic Response	36% to 65%
Minimal Cytogenetic Response	66% to 95%
No Cytogenetic Response	96% to 100%

Major Cytogenetic Response (MCyR) = CCyR + PCyR

These criteria are included in the recent BCSH recommendations on the management of CML [7].

Appendix 2. Health Economic Review

Company submission - economic evidence

1. Description and critique of company submission

The company submission[2] describes an economic model of dasatinib 70mg twice daily treatment compared with imatinib 400mg twice daily in lymphoid blast phase (LB)-CML patients resistant to therapy with imatinib. The same model was used to estimate the cost-effectiveness of the two treatments for Philadelphia chromosome-positive acute lymphoid leukaemia (Ph+ ALL). The models are based on the modelled myeloid blast phase CML presented in a separate company submission of dasatinib in the treatment of CML[2]. This approach assumes that the features of LB-CML and Ph+ ALL are similar to myeloid blast CML in terms of utilities, etc., which is a major limitation of the model. The company submission acknowledges that a number of assumptions have been made in the cost-effectiveness analysis and duly states that: "…results presented…have to be treated with caution due to the paucity of data used"[2].

The model assumes that, following initial treatment, patients with LB-CML and Ph+ ALL enter one of three states: initial best response, no initial response or death. From these three states, patients either remain in their initial LB-CML/Ph+ ALL phase or die. For patients with LB-CML, reversion to an earlier phase of the disease is not possible.

Patients are initially treated with either dasatinib 70mg twice daily or imatinib 400mg twice daily until progression. It is assumed that the prognosis of patients who have a given response to initial treatment is the same irrespective of the initial treatment they receive. This is one of several limitations of the model, as it is feasible that the prognosis of patients resistant to usual dose imatinib could be different when treated with high dose imatinib versus dasatinib. Once progression occurs, patients receive post-failure treatment, which is assumed to be a weighted input of home and hospital palliative care. SCT is indirectly considered as an option for a small proportion of patients (assumed to be 8%).

2. Population

The model estimates the cost-utility of dasatinib in adult patients with LB-CML and Ph+ ALL that is resistant to imatinib used at daily doses less than 600mg. The licensed indication for dasatinib includes patients who are intolerant to imatinib[1]; however, this patient group is not considered in the economic analysis[2].

A hypothetical cohort of 10,000 patients is modelled. Patient age at the start of treatment is taken as 47 years and 48 years, for LB-CML and Ph+ ALL patients, respectively, based on the median age of patients in the two indications enrolled in the CA180-015 trial, which was a single-arm study of dasatinib in patients with LB-CML or Ph+ ALL who were resistant or intolerant to previous imatinib treatment[2].

3. Perspective and time horizon

The model considers costs from the perspective of NHS Wales[2]. No consideration is given to any personal and social service costs/resources, which could feasibly be substantial for a proportion of this patient group.

Each cycle length is one month and a lifetime horizon was chosen for the model[2], which are appropriate for this disease and its treatment.

4. Comparator

The model compares dasatinib 70mg twice daily against imatinib 400mg twice daily in patients resistant to imatinib at doses less than 600mg per day. Other approaches following development of imatinib resistance include combination chemotherapy and possibly SCT.

5. Clinical inputs

5.1 Probability of treatment response and disease progression

5.1.1 Probability of initial treatment response

The company submission states that the initial probabilities of response to treatment for dasatinib are derived from study CA180-015[2]. It is not immediately clear where some of the figures used to estimate the probabilities of initial best response have been derived from, as the figures used in the model appear to have some discrepancies/errors.

For the probability of response with imatinib 400mg twice daily, two studies of imatinib have been cited[16,17], however, there are some anomalies with the data extracted. An example of this is where data on the proportion of patients achieving partial and complete cytogenetic responses are available in one study[17], but not used in the model, which assumes a probability of zero for these parameters.

In addition, these two studies[16,17] appear to have evaluated the efficacy of 400mg and 600mg initial daily doses of imatinib, rather than 400mg twice daily (although a minority of patients did receive doses of 400mg twice daily at least once during the studies). The reliability of these probabilities of initial treatment response is therefore unclear.

5.1.2 Probability of disease progression

The probability of progressing to the next phase of CML or death in the next monthly cycle has been derived from published studies of imatinib. As rates of progression have been reported over different time periods in these studies, monthly probabilities of progression have been derived. Disease progression is separated into short-term (4 to 12 months), and longer term (>12 months) periods; however, as expected survival for imatinib-resistant patients with Ph+ ALL is less than one year, long-term probabilities apply only to those patients with LB-CML[2].

It is unclear how reliable this approach is; it assumes that disease progression rates beyond the initial three months of treatment are independent of the treatment received (i.e. the probability of progression is the same with dasatinib as with imatinib). The results of these studies are based chiefly on imatinib doses of 400–600mg per day in patients who have failed previous treatment. It is not clear how the estimates of probabilities of disease progression derived from these studies relate to the clinical situation being modelled currently (i.e. patients who have demonstrated previous resistance to usual doses of imatinib). There also appears to be an erroneous probability of remaining in the Ph+ ALL phase for patients who have a partial cytogenetic response in the short-term period (4 to 12 months). Based on one of the imatinib studies, this probability is assumed to be 1.0000, which would imply that patients with Ph+ ALL who experience a partial cytogenetic response do not, in the short term, progress directly to death.

5.2 Utility values

The company submission states that, as no estimates of health utility in CML or Ph+ ALL patients were previously available, a study was commissioned to calculate utility weights for the purpose of this analysis[2]. One hundred unaffected individuals (lay population) in the UK

used the time trade off method and EQ-5D to rate the different CML phases (chronic, accelerated and blast phases) and response to treatment. The utility weights are presented for response or no response in each phase; however, no further information is provided to clarify what was considered to be a response to treatment by these unaffected individuals.

It should be noted that this study did not solicit utility values specifically in relation to LB-CML or Ph+ ALL. It has been assumed that the utility values for patients with LB-CML and Ph+ ALL are the same as those solicited in relation to blast phase CML, but the robustness of this assumption is unclear.

Utility weights for a state called 'adverse events' were also elicited in this study (see section 5.4 below).

5.3 Mortality estimation

In the model, patients may die from leukaemia-related causes or non-leukaemia-related causes. The probability of leukaemia-related death is dependent upon patients' current health state and their response to treatment, as assumed from data from studies of imatinib treatment in patients with accelerated or blast phase CML, and Ph+ ALL[2]. The probability of non-CML-related death is based on monthly probabilities of death derived from UK Government Actuary's Department Interim Life Tables for 2003–05[2].

5.4 Adverse events

A utility weight for a state representing a 'standard adverse event' was elicited in the study of 100 unaffected individuals[2] discussed in section 5.2 above. No further details of what constituted a 'standard adverse event' are provided and, it is not clear how adequately this utility weight (value of which is quoted as 0.515) represents the individual serious adverse events that may be experienced by patients with LB-CML and Ph+ ALL who are treated with imatinib or dasatinib.

However, it is unclear how, or whether the utility weight associated with serious adverse events has been included in the analysis. No disutilities associated with any adverse events appear to have been included in the base case analysis, and the one-way sensitivity analyses explore disutilities in the implausible range of -0.1 to -0.99. The costs of serious adverse events were included in the analysis (see section 6 below), but adverse events and their associated costs were assumed only to occur in the first three months of treatment. The company submission states that this is in accordance with clinical experience from the trial programme and is also because of a lack of long term safety data for dasatinib[2].

The probabilities of experiencing each of a range of serious adverse events (used to inform the costs of adverse events occurring only in the first three months) were assumed for dasatinib from trial CA180-006 (a single-arm study of dasatinib in patients with myeloid blast phase CML). For imatinib, the rates of adverse events observed in trial CA180-017 (a non-comparative trial of dasatinib and imatinib in patients with chronic phase CML) have been applied. The company submission states that the use of adverse event data for imatinib from a clinical trial of patients with chronic phase CML may underestimate the true incidence of serious adverse events with imatinib in patients with LB-CML or Ph+ ALL, as the latter group of patients are sicker[2].

It is unclear why the serious adverse event probabilities were not taken from trial CA180-015. Furthermore, there appear to be some discrepancies in the rates of some dasatinib adverse events from trial CA180-006 in patients with myeloid blast phase CML (and used in the model) and those actually reported in the trial of dasatinib in patients with LB-CML and

Ph+ ALL (trial CA180-015). For example, the model uses a rate of thrombocytopenia of 13.1% and neutropenia of 11.1% for dasatinib[2], but according to a recent presentation of results for trial CA180-015, in patients with Ph+ ALL, the absolute baseline-subtracted rates of thrombocytopenia and neutropenia were 32% and 61%[12].

The probabilities of adverse events appear not to have been explored in sensitivity analyses, so the influence of serious adverse events on the cost-effectiveness estimates is uncertain.

6. Healthcare resource utilisation and cost

Resource use (excluding imatinib and dasatinib drug treatment costs) in the treatment of LB-CML and Ph+ ALL has been estimated on the basis of the opinion of two haemotologists, one from Wales and one from Scotland. Published unit costs inflated to 2006 prices have been applied to each unit of resource.

Unit costs of drug treatment with dasatinib and imatinib have been obtained from the British National Formulary. Post-failure treatment has been assumed to comprise 25% of patients receiving palliative care at hospital and 25% of patients receiving chemotherapy (both costed using previously published costs for imatinib treatment, inflated to current prices), and 50% receiving care at home, which has not been costed. There is no indication that this assumed post-failure treatment has been verified externally.

The costs of adverse events (but not the associated disutilities) occurring in the first three months of treatment have been incorporated into the base case model[2]. These are stated to be based on the rates of serious adverse events noted in the clinical trials and the application of costs based on key opinion leader estimates. As discussed in section 5.4 above, there appear to be some unexplained discrepancies in the rates of some adverse effects (e.g. thrombocytopenia and neutropenia) used in the model[2] and those reported elsewhere. These adverse events are amongst the most expensive to manage as estimated by the key opinion leader. The impact of these discrepancies is difficult to ascertain, as the model does not explore the probability of serious adverse events in sensitivity analyses.

Personal and social service costs/resources, which could feasibly be substantial for this patient group, are not considered.

7. Discounting

All costs and outcomes were discounted at 3.5% per annum in the base case analysis[2], which is the preferred discount rate. Other discount rates were explored in sensitivity analyses.

8. Results

8.1. Base-case

The increment costs/QALY for treatment with dasatinib 70mg twice daily compared with imatinib 400mg twice daily are presented in the following table[2]:

	LB-CML	**Ph+ ALL**
Incremental costs	£86,559	£4,971
Incremental QALYs	1.31	0.08
ICER	**£66,158**	**£61,533**
Life time horizon, all values discounted at 3.5%		

8.2. Sub-group analysis
No other sub-group analyses were undertaken.

9. Sensitivity analysis
A series of one-way sensitivity analyses were carried out to determine the impact of various individual parameters on the model outputs. Probabilistic sensitivity analyses were also conducted[2].

9.1 One-way sensitivity analyses
It is important to note that the probabilities of treatment response and progression, the probabilities and costs of adverse events, and the daily dose of dasatinib were not explored in one-way sensitivity analyses.

9.1.1 LB-CML
None of the one-way sensitivity analyses that were conducted reduced the ICER to less than £49,950 per QALY gained. The model appeared most sensitive to the assumptions on utilities associated with response to treatment (varying utilities by ±20% resulted in the ICER ranging from £54,632 to £83,848 per QALY gained) and the discount rates used for costs and benefits (adopting respective discount rates of 6% and 1.5% led to a 25% decrease in the ICER, to £49.953 per QALY gained). The model was also sensitive to the assumptions of disutility associated with adverse effects, which is relevant given the uncertainty in the assumptions outlined in section 5.4 above, however the implausible range -0.1 to -0.99 was explored (at a value of -0.1 the ICER increased to £69,311 per QALY gained). Reducing the daily dose of imatinib from 800mg to 600mg increased the ICER to £70,251 per QALY gained[2].

9.1.2 Ph+ ALL
None of the one-way sensitivity analyses that were conducted reduced the ICER to less than £51,230 per QALY gained. The model appeared to be very sensitive to the assumptions of the utilities associated with response to treatment (varying utilities by ±20% resulted in the ICER ranging from £51,231 to £77,020 per QALY gained) and disutility associated with adverse events (the implausible range explored was -0.1 to -0.99, but at a value of just -0.1 the ICER increased to £232,593 per QALY gained). Reducing the daily dose of imatinib from 800mg to 600mg increased the ICER to £81,560 per QALY gained[2].

9.2 Probabilistic sensitivity analysis
Separate probabilistic sensitivity analyses (PSA) have not been conducted for LB-CML and Ph+ ALL. Instead, the PSA as conducted for the blast phase CML in a separate company submission of dasatinib in CML[15] has been assumed. The relevance of the analysis is therefore questionable.

Company submission - budget impact analysis

1. Description and critique of company submission

The company submission states that the budget impact analysis compares the impact of the use of dasatinib for the treatment of LB-CML and Ph+ ALL in imatinib-resistant and imatinib-intolerant patients with the use of increased doses of imatinib[2]. It should be noted that the use of increased doses of imatinib are unlikely to be a viable option for imatinib-intolerant patients. As there is a lack of epidemiological data (e.g. regarding the incidence of LB-CML and the imatinib failure rate in patients with Ph+ ALL), there are several assumptions made based on data relating to myeloid blast CML. The model assumes 100% uptake of dasatinib in patients who are resistant to or intolerant of dasatinib.

2. Perspective and time horizon

The perspective adopted by the budget impact analysis is that of NHS Wales, with a five-year time horizon starting in 2008[2]. Only drug acquisition costs are considered in the analysis.

3. Data sources

3.1. Incident cases

The company submission indicates that no LB-CML incidence data is available. Based on data from the Welsh Cancer Surveillance and Intelligence Unit[18], there were 40 new cases of CML diagnosed in Wales in 2005[2]. According to the data provided, this appears to be fairly consistent over the period 2000 to 2005[18]. The company submission quotes the NICE technology appraisal of imatinib[4] as indicating that around 5% of CML patients are in the blast phase (approximately 2 patients), which could include lymphoid and myeloid blast phase CML. The company submission states that 12 adults were diagnosed with ALL in 2005[2,18], of which around 25% were estimated to be Ph+ (i.e. 3 patients). However, incidence rates are not used in the model, on the basis that the disease prevalence captures the flow of new patients and mortality[2].

3.2. Prevalent cases

The company submission states that there will be an estimated 5 patients with LB-CML in 2008. The company submission states that this is based on an estimated 148 adults with CML in Wales in 2003 (using the prevalence rate for England and Wales, as quoted in the NICE technology appraisal of imatinib[4], and applying this to the population of Wales), which has been increased by 10% per year from 2003 to 2008 on the basis of survival data from Novartis in relation to imatinib[15]. However, this data is not verifiable and it is unclear how the 5 patients with LB-CML are derived from the 256 patients with CML.

For Ph+ ALL, the company submission states that there were 26 adult patients in 2003. No prevalence figure has been provided for 2008.

3.3. Market share

Of the 5 patients with LB-CML, 4 are claimed to be suitable for dasatinib. However, the company submission states that in 2008 around 13 patients with Ph+ ALL will be suitable for dasatinib, which it is stated may be an over estimate according to the opinion of Welsh haematologists (no further details provided)[2]. The total number of patients suitable for dasatinib in 2008 is therefore quoted as 17 (13 Ph+ ALL patients + 4 LB-CML patients).

The company submission then states that a maximum of 23 patients in 2008 and 24 patients in each year 2009–12 will receive dasatinib. This is reported to be based on a number of assumptions around the treatment of patients with myeloid blast CML and data from surveys which are not verifiable. The estimates of the number of patients to be treated in 2008 appear to be inconsistent with the figures quoted previously in the company submission. Therefore, the number of patients quoted as likely to be eligible for treatment with dasatinib must be treated with caution.

3.4. Rates of adoption

The model assumes that patients newly diagnosed with CML would be considered for BMT, then imatinib, and then dasatinib[1]. It assumes 100% uptake in patients who are resistant to or intolerant of imatinib in the base-case and a slower rate of uptake is explored in another scenario.

3.5. Displaced medicine(s)

The model assumes that, following imatinib resistance or intolerance, dasatinib is the only alternative. High dose imatinib for resistant patients and low dose imatinib for intolerant patients is potentially displaced. The company submission provides figures for the doses of imatinib used based on a physician survey. Well managed patients are assumed to receive imatinib 600mg daily. Resistant patients with blast CML are reported to receive higher doses, on average 721mg. Intolerant patients in any CML phase are reported to receive 300mg daily and these doses have been assumed to apply to patients with Ph+ ALL[2]. This is data on file and cannot be verified. Dasatinib recipients are assumed to receive 70mg twice daily in all phases.

4. Results

4.1. Base-case

The budget impact of the use of dasatinib instead of imatinib in imatinib-resistant or intolerant patients has been estimated for each of the five years from 2008 to 2012. The cost of imatinib treatment in the absence of dasatinib as an alternative has been calculated by applying the cost per mg of imatinib to the average daily doses of imatinib used by resistant, intolerant patients and well managed patients (as outlined in section 3.5 above). The cost of dasatinib if used in all imatinib resistant and intolerant patients is estimated by applying the cost of dasatinib 70mg twice daily to each of these patients.

Assuming 100% uptake, the cost of using dasatinib instead of imatinib is estimated to save approximately £28,800 in 2008 and £29,300 in each of years 2009–12 (i.e. dasatinib treatment is less expensive than imatinib treatment).

These figures must be viewed with caution given the range of assumptions used, inconsistencies in calculation of patient numbers, etc.

4.2. Sub-group analysis

No sub-group analysis has been conducted.

5. Sensitivity analysis

A scenario of a slower rate of uptake has also been modelled. If uptake is 50% in 2008, 75% in 2009 and 100% in subsequent years, the cost savings with the use of dasatinib instead of imatinib would be £14,400 in 2008, £22,000 in 2009 and £29,300 in 2010–12.

No further sensitivity analysis has been conducted.

Appendix 3. Clinical Expert Summaries – summarised in 9.4.

Appendix 4. Patient Interest Group submission(s) – supplied as a separate document

Appendix 5. Company written response – supplied as a separate document.