All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

AWMSG ADVICE SUPERSEDED BY NICE GUIDANCE (TA241)

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Final Appraisal Report

Dasatinib (Sprycel®) for the treatment of chronic, accelerated or blast phase chronic myeloid leukaemia

Bristol Myers Squibb

Advice No: 1307 – December 2007

Recommendation of AWMSG

Dasatinib (Sprycel®) is recommended for restricted use within NHS Wales for the treatment of adults with chronic phase chronic myeloid leukaemia (CML) and accelerated phase CML where there is resistance or intolerance to prior therapy including imatinib mesilate. The use of dasatinib for blast phase is not recommended.

Resistance to imatinib is defined in accordance with the European LeukaemiaNet criteria and on completion of mutation analysis.

Intolerance is defined as a patient experiencing prior grade 3/4 toxicity, in accordance with the National Cancer Institute Common Toxicity Criteria, to imatinib despite receiving the lowest clinically effective dose.

Dasatinib (Sprycel®) should only be initiated by specialists experienced in the treatment of chronic myeloid leukaemia.

Dasatinib (Sprycel®) is not presently recommended for shared care.

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

1.0 RECOMMENDATION OF AWMSG:

Date: 11th December 2007

The recommendation of the AWMSG is:

Dasatinib (Sprycel®) is recommended for restricted use within NHS Wales for the treatment of adults with chronic phase chronic myeloid leukaemia (CML) and accelerated phase CML where there is resistance or intolerance to prior therapy including imatinib mesilate. The use of dasatinib for blast phase is not recommended.

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Dasatinib (Sprycel®) should only be initiated by specialists experienced in the treatment of chronic myeloid leukaemia.

Dasatinib (Sprycel®) is not presently recommended for shared care.

Key factors influencing the recommendation:

There are no published randomised controlled trials directly comparing dasatinib with other current therapeutic treatment options for patients with CML.

The economic case for the use of dasatinib has not been clearly demonstrated in patients with blast phase CML.

Additional note:

For blast phase disease in CML, AWMSG suggests patients should be considered for entry into clinical trials to clarify the position of further therapy.

2.0 PRODUCT DETAILS:

2.1 Licensed indication:
Dasatinib (Sprycel®) is licensed for the treatment of adults with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy including imatinib mesilate[1].

2.2 Dosing:
The recommended starting dose is 100mg once daily for chronic phase CML and 70mg twice daily for accelerated or blast phase CML. In clinical trials the dose could be escalated according to haematological response to 140mg once daily for chronic phase CML and 100mg twice daily for accelerated or blast phase CML[1].

Treatment is continued until disease progression or until it is no longer tolerated by the patient[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 chronic, accelerated and blast phase CML. Dasatinib is also licensed for the treatment of acute lymphoblastic leukaemia (ALL) and lymphoid blast (LB) CML which is the subject of AWMSG appraisal number 1407.

CML is a haematopoietic stem cell disorder with an incidence of around 1 or 2 cases per 100,000 population per year; men are predominantly affected, the median age at diagnosis is around 65 years[3]. Ninety-five percent of patients have a chromosome abnormality caused by reciprocal translocation of genetic material between chromosomes 22 and 9, known as 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 the bone marrow producing an excessive number of abnormal stem cells, eventually suppressing the production of normal white blood cells[2].

There are three stages (or phases) of this progressive disease: chronic, where patients may remain for several years, accelerated, which may last 6-18 months and finally blast phase (or crisis) (BC) which has a poor prognosis[2,4]. The latter two represent advanced stages of the disease and are more resistant to treatment. Most patients are diagnosed in the chronic phase of the disease through routine testing.

In 2003 the National Institute for Health and Clinical Excellence (NICE) recommended imatinib as first-line treatment for people with Philadelphia-chromosome positive (Ph+) 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 recommended the use of continuing imatinib where treatment has failed to stop the advancement of the disease in the context of further clinical study only[5]. NICE advice is due to be reviewed in 2009 pending the results of ongoing studies[6].

Imatinib is very effective at treating newly diagnosed CML, with complete haematological response (CHR) rates of 95% and complete cytogenetic response (CCyR) rates of 74% reported[7]. Patients with a CCyR at 12 months have a significant reduction in disease progression[8]. However resistance can develop. Follow up data from the IRIS study (imatinib versus interferon alfa plus cytarabine) estimates an overall relapse rate of 17% at five years with an estimated 6% of patients progressing to accelerated phase or BC[8].

An observational analysis conducted in Texas by Kantarjian and colleagues reported earlier this year estimated outcome survival data for 420 patients with CML (all phases) who had failed imatinib due to resistance or recurrence (n=374) or toxicity (n=46). The estimated three-year survival data was 72% in 88 patients who progressed in chronic phase, 30% in 130 patients who progressed in accelerated phase and 7% in 156 patients who progressed in blast phase. Survival in the chronic phase of the disease was better for those patients who went on to receive nilotinib or dasatinib (n=40) versus those who went on to receive haematopoietic stem cell transplantation (SCT) (n=10) or other treatments (n=68), with estimated two-year survival rates 100% versus 72% versus 67%, respectively, P=0.01. However survival was not prolonged for those patients in advanced phases of the disease. Treatment was not found to be a factor in improved survival rates, the authors concluded that this may have be due to the short follow up[9].

In 2006 the European LeukaemiaNet published consensus recommendations on the management of CML which included a definition of imatinib treatment failure (appendix one, table one). For those who have failed treatment with imatinib the group recommend allogeneic SCT or alternatively increasing the dose of imatinib to 600-800mg/day. This is providing the patient has previously tolerated 400mg/day and that their resistance to imatinib is not due to a BCR-ABL mutation with a high level of insensitivity to imatinib. In the case of intolerance or toxicity the options are allogeneic SCT or interferon alfa with or without low dose cytarabine. These guidelines were developed before the licensing of dasatinib[10].

More recently the British Committee for Standards in Haematology published their recommendations for the management of Ph+ CML. For patients failing to respond to imatinib they advocate the use of second generation tyrosine kinase inhibitors (such as dasatinib) or allogeneic SCT for patients with suitable donors. Interferon alfa or hydroxycarbamide may have a role in patients still in the chronic phase of the disease who have failed imatinib and a second generation tyrosine kinase inhibitor[11].

4.0 EXECUTIVE SUMMARY:

4.1 Review of the evidence on clinical effectiveness

The company have based their submission on four Phase II trials; only one of these was a comparative trial however the study was not designed to assess statistically significant differences between treatment groups. Patients with chronic phase Ph+ CML were randomised to receive dasatinib or high dose imatinib, which would appear to be a suitable comparator based on currently available treatment options. With a median follow up of 15 months (range: 1 to 21 months), a major cytogenetic response (MCyR) was seen in 52% of dasatinib treated patients and 33% of high dose imatinib treated patients. During the 15 month follow up 28% and 82% of dasatinib and imatinib treated patients respectively were considered to be treatment failures. The median time to treatment failure was 3.5 months for imatinib and had not been reached for dasatinib at 15 month follow up. The remaining three trials are

non-comparative making it difficult to put their results in context but provide evidence of response to dasatinib despite prior intolerance or resistance to imatinib in patients with chronic and advanced stages of the disease.

In the comparative dasatinib and imatinib trial, pleural effusion and grade 3-4 thrombocytopenias were reported more commonly with dasatinib. The European Public Assessment Report (EPAR) for dasatinib comments that most of the identified risks were manageable and adds that important long-term safety data is missing. Treatment with imatinib was associated more commonly with gastrointestinal events, fluid retention and muscle spasm.

4.2 Review of the evidence on cost-effectiveness

The economic model presented compares dasatinib (70mg twice daily) against high dose imatinib (400mg twice daily) in patients with chronic, accelerated and blast phase CML that is resistant to usual dose imatinib. The use of dasatinib in patients intolerant of imatinib has not been considered. Due to a lack of data, the model employs a number of assumptions related to disease progression, the utility values associated with response to treatment, and the impact and costs of adverse events. Initiation of dasatinib treatment in the accelerated and blast phases of CML results in high incremental costs per QALY that exceed conventional thresholds of cost-effectiveness under the most optimistic parameter values tested. In contrast, initiation of dasatinib treatment in the chronic phase dominates (i.e. is more effective and less expensive than) the alternative strategy of high dose imatinib. This result in the chronic phase of CML appears insensitive to the assumptions tested, with the significant exception of the dose of imatinib used in these patients. Using a daily imatinib dose of 600mg, instead of 800mg, has the effect of moving dasatinib from being dominant over imatinib to having an incremental cost per QALY of over £57,000.

The economic case for the use of dasatinib has not been demonstrated in patients intolerant of imatinib, or for accelerated and blast phase CML with resistance to usual dose imatinib. Additionally, dasatinib may not represent an efficient use of healthcare resources in patients in the chronic phase CML who are resistant to usual doses of imatinib but are capable of being well managed on daily doses of imatinib of less than 800mg.

5.0 LIMITATIONS OF DECISION CONTEXT:

- There are no published Phase III randomised controlled trials directly comparing dasatinib with current therapeutic treatment options for CML.
- No trials have been undertaken in patients with hepatic or renal impairment, 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:

Four Phase II clinical studies form the basis of the company submission, the **S**RC/ABL **T**yrosine kinase inhibition **A**ctivity **R**esearch **T**rials of BMS-354825 or 'START' programme. A fifth study in the programme, 'START L' (CA180015) is considered under a separate submission for PH+ ALL and LB-CML to AWMSG (advice no. 1407).

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 two, details the cytogenetic response criteria for the START programme.

Chronic disease:

START R (CA180017)

This was a multicentre open-label non-comparative study in adult patients with chronic phase Ph+ CML with resistance to imatinib 400-600mg/day[12]. Two-thirds of patients had received treatment with imatinib 600mg/day; 40% of patients had received imatinib for over 3 years. Patients with an ECOG score of 0-1 were randomised 2:1 to receive dasatinib 70mg twice daily (n=49) or imatinib 400mg twice daily (high-dose, n=101); those who failed to respond to or were unable to tolerate their assigned treatment could crossover to the alternative treatment.

The primary end point was major cytogenetic response (MCyR) at 12 weeks.

Table one. 12-week response rates for START R, dasatinib versus. high dose imatinib

End points: Haematological and cytogenetic response rates	Dasatinib (n=101)	Imatinib (n=49)	Treatment Difference
MCyR	36%	29%	7% (95% CI: -9.8 to 22.2%, P=0.4025)
CCyR	22%	8%	14% (95% CI: 0.6 to 24.8%, P=0.041)
CHR	93%	82%	11% (95% CI: -0.7 to 25.2%, P=0.034)

Major Cytogenetic Response (MCyR); Complete Cytogenetic Response (CCyR) Complete haematological response (CHR)

After a median follow up of 15 months (range 1-21 months), the major cytogenetic response (MCyR) increased to 52% and 33% for dasatinib and high dose imatinib treated patients respectively, corresponding to a treatment difference of 20% (95% CI: 2.6 to 35.3%, P=0.023). The complete cytogenetic response (CCyR) increased to 40% for the dasatinib group and 16% for the high dose imatinib group, a treatment difference of 23% (95% CI: 7.7 to 36.5%, P=0.004). Treatment failure due to disease progression, lack of response or coming off therapy was documented for 28% of patients randomised to dasatinib and 82% randomised to high dose imatinib[2,12]. The median time to treatment failure was 3.5 months for imatinib (95% CI: 3.3 to 3.8 months) and had not been reached for dasatinib[12].

For those patients who crossed over treatment, 19/39 patients (49%) achieved MCyR when switched from imatinib to dasatinib compared with 1/15 patients (7%) who received imatinib after treatment failure with dasatinib (P=0.006). Of the patients with imatinib resistant mutations detected at baseline, more patients achieved the primary end point, MCyR in the dasatinib group but this was not significantly higher than the imatinib group[12].

Points to note:

- Though treatment differences have been included in the results this study was not powered to assess comparative efficacy

- Screening for mutations was not required for enrolment. However more patients in the dasatinib arm had a BCR-ABL mutation when compared with the high dose imatinib arm.
- Imatinib intolerant patients were excluded from entering the study
- Dasatinib dose modifications were allowed for disease progression or lack of response or to manage drug toxicity. The imatinib dose could be reduced to 600mg/day provided the patient had not previously received that dose prior to study entry. The median daily dose of dasatinib was 103mg (range: 38 to 175mg) and 796mg (range: 358 to 800mg) for imatinib.
- 54 patients crossed over treatment (15 from the dasatinib group and 39 from the high dose imatinib group). Of the evaluable patients, 17/38 patients subsequently achieved a MCyR with dasatinib and 2/13 with high-dose imatinib (P=0.063).

START C (CA180013)

This open-label single-arm study was undertaken in adult patients with chronic phase Ph+ CML who had disease resistant to over 600mg/day (n=288) or were intolerant to 600mg/day or less of imatinib (n=99)[13, 14]. The primary endpoint was MCyR. Results have been published for an initial cohort of 186 patients at a median follow up of 8.3 months. Follow up data which includes all 387 patients at median follow up of 15.2 months has been presented at conference and is included here for completeness. This information has not been published in a peer reviewed publication.

Table two. Response rates for START C

Endpoints: Haematological and cytogenetic response rates	8.3 months follow up[13]			15.2 months follow up[14]		
	Intolerant (n=59)	Resistant (n=127)	Total (n=186)	Intolerant (n=99)	Resistant (n=288)	Total (n=387)
MCyR	80%	39%	52%	80%	52%	59%
CCyR	64%	28%	39%	75%	40%	49%
CHR	9%	87%	90%	n/a	n/a	91%

One-third of patients are no longer on treatment. Three of the 99 imatinib-intolerant and 37 of the 287 imatinib-resistant patients experienced disease progression. A total of 14 patients had died at the time of the 15 month analysis[14].

Points to note:

- Dose escalations up to 90mg twice daily were allowed for patients who showed evidence of disease progression or lack of response. Similarly dose reductions were allowed for toxicity. The median dasatinib dose was 101mg/day (range: 11-171mg/day). The majority of patients required dose reduction or interruption at some point in the trial.
- The majority of patients with imatinib resistant disease had received daily doses of imatinib exceeding 600mg/day; 35% had shown a MCyR as their best cytogenetic response with imatinib. Of those with prior imatinib intolerance, 44% had shown a MCyR as their best cytogenetic response; the majority of whom had received imatinib 400-600mg/day.

Advanced disease:

START A (CA180005) – Accelerated Phase

This was an open-label single-arm study in patients with accelerated phase CML intolerant to imatinib 400mg or more/day or who had progressed to accelerated phase despite imatinib 400mg or greater/day, or were in accelerated phase and had

failed to achieve a haematological response, or were no longer responding to imatinib 600mg or more/day [15,16]. Though patients had been extensively pre-treated the majority had an Eastern Cooperative Oncology Group (ECOG) score of 0-1 indicating the patients were reasonably active. Interim data has been published for 107 patients at 8 months follow up[15]. Results presented at a recent conference are included here and provide data on all patients enrolled onto the study[16]. This information has not been published in a peer reviewed publication.

Table three. Response rates for START A

End points: Haematological and cytogenetic response rates	8 months follow up[15]			14.1 months follow up[16]		
	Intolerant n=8	Resistant n=99	Total n=107	Intolerant n=13	Resistant n=161	Total n=174
MaHR	63%	65%	64%	n/a	n/a	64%
CHR	38%	39%	39%	n/a	n/a	45%
NEL	25%	25%	25%	n/a	n/a	19%
MCyR	13%	34%	33%	38%	38%	39%
CCyR	13%	25%	24%	38%	31%	32%

Major haematological response (MaHR) = CHR + NEL; No evidence of leukaemia (NEL)

The median follow up was 14.1 months (range: 0.1 to 21.7 months). Mean daily dose was 126mg (range: 32-196mg). The majority of patients required dose reduction or interruption during their treatment[16].

Points to note:

- Previous overall rate of MCyR with imatinib was 33%[16].
- 52% (90/174) of patients had discontinued treatment at the time of this analysis: 22% (38/174) due to disease progression and 8% (14/174) due to drug toxicity[16].
- PFS and overall survival (OS) have not been reached[16].

START B (CA180006) – Blast Phase

This was an open-label single-arm multinational study of dasatinib in adult patients with myeloid BC CML resistant to (>90%) or intolerant of (<10%) imatinib[17, 18]. Results for 74 of the 109 patients entered into the study have been published[17]. More recently data for all 109 patients have been presented at conference[18]. This information has not been published in a peer reviewed publication.

Table four. Response rates for START B

End points: Haematological and cytogenetic response rates	8 months follow up[17] n=74	1-21 month* follow up[18] n=109
OHR (primary end point)	53%	50%
MaHR (primary end point)	34%	34%
CHR	26%	27%
NEL	8%	7%
MiHR	19%	16%
MCyR	31%	33%
CCyR	27%	26%

Overall haematological response (OHR) = MaHR + MiHR; MaHR = CHR + NEL; Minor haematological response (MiHR)

*No median follow up reported in the presentation.

Of the 37 patients who reached MaHR, 7 had progressed when results of this study were reported. Median PFS was 6.7 months and median OS was 11.8 months[18].

Points to note:

- Prior to enrolment, 50% of patients had received imatinib over 600mg/day and 41% had received imatinib for over 12 months[18].
- Majority of patients had an ECOG score of 0-1[18]

6.2 Safety:

The most frequently (10% and over) reported adverse events of patients during clinical trials with dasatinib included gastrointestinal disorders, rash, fluid retention, fatigue, asthenia, pyrexia and dyspnoea. The majority of events were considered to be drug-related. Important identified risks are toxicity regarding the gastrointestinal system and fluid retention. Approximately 14% of patients experienced a pleural effusion considered to be related to dasatinib. Haemorrhage occurred in one-third of patients treated with dasatinib, the majority of these events were manageable. The EMEA have accepted a risk management plan, which includes risk minimisation activities, with regard to the potential safety concerns highlighted. The European Product Assessment Report (EPAR) states that there is important missing information regarding long-term safety data with dasatinib[4].

The START R trial included patients receiving dasatinib or high-dose imatinib[12]. More patients in the trial discontinued imatinib than dasatinib and therefore the length of exposure to each treatment differed. In addition imatinib intolerant patients were excluded from the trial. Any direct comparisons in terms of adverse event incidence rates should therefore be interpreted with caution. The majority of adverse events were considered by the authors of the study to be mild to moderate in intensity and resolved with no treatment or supportive care. Those reported more commonly with dasatinib than with imatinib were:

- Pleural effusions 17% versus 0%; no grade 4 pleural effusions were observed. Patients were successfully managed with dose interruption, diuretics and/or pulse steroid therapy.
- Grade 3-4 thrombocytopenia 56% versus 14%; these were reversible and responded to dose adjustments. Transfusions of packed red blood cells and platelets were required more frequently in the dasatinib group.
- Other adverse events more commonly reported with dasatinib included diarrhoea, headache, fatigue and dyspnoea.

Overall gastrointestinal adverse events, fluid retention and muscle spasm were more common with imatinib.

According to the EPAR for dasatinib, of the 59 imatinib-intolerant patients entered onto the START C study, 41 (69%) had no recurrence of the toxicity that caused intolerance to imatinib. Eighteen (31%) experienced toxicities while on treatment with dasatinib that were similar to what they had experienced while receiving imatinib[4].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES:

7.1 Comparator medications:

Where imatinib treatment fails, high dose imatinib therapy may be an option where mutation analysis suggests the presence of only mildly resistant mutations and

according to patient tolerability. However response may be short-lived and alternative treatments required[11].

Allogeneic SCT would be an option for a limited sub-population of patients. Alternatively patients may receive experimental therapies and/or be eligible for entry into clinical trials.

A number of therapies are under investigation for this condition, the one closest to licence is nilotinib, a tyrosine kinase inhibitor like dasatinib that has also been shown to be effective in imatinib-resistant CML and is active against imatinib-resistant mutations with the exception of T315I (as is dasatinib). Agents active against T315I are in development.

7.2 Comparative effectiveness:

Only one Phase II study has compared dasatinib with an alternative treatment (high dose imatinib), however the study was not powered to assess statistically significant differences between groups. This study differs from the other CML trials in that patients were excluded from the trial if they were intolerant to imatinib and patients were able to crossover to alternative treatment. All remaining trials have been non-comparative. As different phases of CML have been included in the START programme definitions of response tended to vary between studies.

Patients who were intolerant of imatinib tended to have greater response rates to dasatinib than those who were resistant to imatinib. However the effect of baseline mutations appeared not to affect overall response to dasatinib with the exception of the T315I mutation. Mutation analysis may prove useful in identifying future treatment options for patients.

Looking at the median age of patients included in the trials, they tended to be relatively young, with an ECOG score of 0-1. Patients with cardiovascular disease, liver and renal impairment were not eligible for study entry.

A wide range of doses have been used in the Phase II clinical trials, patients with advanced disease tended to require higher median doses then those with chronic disease. Ongoing Phase II and III studies are looking at different doses and dosing schedules [2, 19]. This has recently led to a license change in the starting dose recommendations for chronic phase CML. Further information is provided in the company's submission and response.

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE:

8.1 Overview of the key economic issues for AWMSG to consider

The key economic issues for AWMSG to consider are whether the additional benefits offered by dasatinib over the relevant comparator justify the associated costs and whether the total budgetary impact of supporting the use of clofarabine is acceptable.

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 CML.

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 was designed to assess the cost-utility of dasatinib in adult patients with chronic, accelerated or blast phase CML resistant to imatinib used at daily doses of <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]. In the model, patients begin treatment in one of three phases of CML: chronic, accelerated, or blast phase. 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 three sponsor clinical studies. The probabilities of response with imatinib 400mg twice daily in the chronic phase is stated to have been derived from study CA180-017, but for the accelerated phase and the blast phase, two studies of imatinib have been cited[12, 20]. These two studies appear to have evaluated the efficacy of 400mg and 600mg daily doses of imatinib, rather than 400mg twice daily (although a minority of patients in the studies did use at least one dose of 400mg twice daily). 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 a range of 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 is feasible that the prognosis of patients resistant to usual dose imatinib could be different when treated with high dose imatinib versus dasatinib. There appear to be some issues with the consistency of the probabilities used from a range of different sources.

A study was commissioned to calculate utility weights for the purpose of this analysis[2]. However, no information is provided to clarify what was considered to be a response to treatment or details of how serious adverse events were described to the study participants. No utility values associated with any adverse events have been included in the base case analysis. There appear to be some discrepancies in the rates of some adverse events used in the model and those reported in the published paper and 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 CML drug treatment costs) has been estimated on the basis of the opinion of two haematologists, 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. Probabilistic sensitivity analyses (PSA) were also conducted, but these also appear not to have included the probabilities and costs of adverse events, and the daily dose of drugs used.

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 starting in each phase of CML are presented in table five.

Table five. Incremental cost per QALYs for treatment with dasatinib (70mg twice daily) versus imatinib (400mg twice daily)

	CML phase		
	Chronic	**Accelerated**	**Blast**
Incremental costs	-£10,501	£98,550	£59,941
Incremental QALYs	0.64	2.21	0.92
ICER	**Dominant**	**£44,538**	**£63,817**

Life time horizon, all values discounted at 3.5%

In the one-way sensitivity analyses of the chronic phase CML model, the outputs appeared insensitive to most parameters tested. However, decreasing the daily dose of imatinib used from 800mg to 600mg had a dramatic effect, moving dasatinib from being dominant over imatinib to having an ICER of £57,465. This is an important finding as, according to the company submission, data from a survey of physicians indicates that imatinib resistant patients receive, on average, 619mg daily in the chronic phase[2] (and not 800mg daily as modelled in the base case analysis).

The probabilistic sensitivity analysis indicated that dasatinib was more cost-effective than imatinib, when used in the chronic phase of CML, in over 90% of cases when the willingness to pay was £20,000 per QALY gained or more.

For the accelerated phase, dasatinib is not cost-effective below a willingness to pay of around £38,000 per QALY. To be cost-effective in 50% of cases, the willingness to pay would need to be around £45,000 per QALY gained. For the blast phase, dasatinib is not cost-effective below a willingness to pay of around £48,000 per QALY gained. To be cost-effective in 50% of cases, the willingness to pay would need to be around £64,000 per QALY gained.

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, 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, in 2008, there will be 256 patients with CML in Wales. This is based on the application of the prevalence rate for England and Wales in 2003[5] to the current population of Wales and increasing the figure by 10% per year from 2003 to 2008 to account for a reported increased survival of patients following the introduction of imatinib[2]. This is not verifiable from the data and references provided. The company submission then adds 6 patients to this figure of 256 patients, although it is not clear why this has been done. The resultant figure of 262 patients with CML in Wales is then claimed to remain constant from 2008 to 2012. Two hundred and fifty-one patients with CML are expected to be treated with imatinib in Wales in 2008. No reference is provided to verify this.

The company submission estimates the number of people likely to be prescribed dasatinib as 86 patients in 2008, rising to 88 patients in years 2009-12.

The model assumes that patients newly diagnosed with CML would be considered for SCT, 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 average doses of imatinib used based on a physician survey. Well managed patients are assumed to receive imatinib 400mg once daily in the chronic phase and 600mg once daily in the accelerated and blast phases. Resistant patients are reported to receive higher doses, on average 619mg once daily in the chronic phase, 697mg in the accelerated phase and 721mg in the blast phase. Intolerant patients in any phase are reported to receive 300mg once daily. 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. 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 incremental cost of using dasatinib instead of imatinib is estimated as approximately £96,000 in 2008 and £99,000 in each of years 2009–12.

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 incremental cost of dasatinib would be £48,000 in 2008, £74,000 in 2009 and £99,000 in 2010–12.

9.0 ADDITIONAL INFORMATION:

9.1 Guidance and audit requirements:

- The British Committee for Standards in Haematology have recently published their recommendations on the management of BCR-ABL positive CML which advocate the use of dasatinib (and other second generation tyrosine kinase inhibitors) in patients who have failed or who are no longer responding to treatment with imatinib[11].
- Dasatinib would not be deemed suitable for shared care. Treatment initiation, monitoring and supervision should be retained under Specialist care.

9.2 Previous NICE advice:

In 2003 NICE recommended imatinib as first-line treatment for people with Ph+ 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 (see also section 3.0)[5].

9.3 Ongoing studies[2]

- Paediatric study
- Once daily versus twice daily - presented at ASH 2006
- Dasatinib versus imatinib (high-dose) in patients with sub-optimal response to imatinib
- First-line use in patients with CML - presented at ASH 2006

9.4 Medical Expert

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

First line treatment for (Ph+) CML in NHS Wales is imatinib, as per NICE guidance. Patients who are intolerant or resistant to imatinib are offered BMT if a suitable option. Alternative tyrosine kinase inhibitors may have a role where BMT is unsuitable.

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

Estimates of population likely to require treatment are below those quoted in the company submission.

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. Definition of treatment failure or suboptimal response for previously untreated patients with CML who are treated with imatinib 400mg daily[10]:

Time (since diagnosis)	Failure	Suboptimal response	Warnings
0 months	n/a	n/a	High risk, del9q+, ACAs in Ph+ cells
3 months	No haematological response (stable disease or disease progression)	Less than complete haematological response	n/a
6 months	Less than complete haematological response, no complete cytogenetic response (Ph+ > 95%)	Less than partial cytogenetic response (Ph+>35%)	n/a
12 months	Less than partial cytogenetic response (Ph+ > 35%)	Less than complete cytogenetic response	Less than major molecular response
18 months	Less than complete cytogenetic response	Less than major molecular response	n/a
Anytime	Loss of CHR, loss of complete cytogenetic response, mutation (highly resistant)	ACA in Ph+ cells, loss of major molecular response, mutation (low level resistance)	Any rise in transcript level; other chromosome abnormalities in Ph- cells

Table two. Cytogenetic Response Criteria for START trials[2]:

Response	Philadelphia (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[11].

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 CML patients resistant to therapy with imatinib. The model does not include an analysis of dasatinib in patients who are intolerant to imatinib. A Markov model structure was adopted, which is an appropriate approach to the modelling of this disease. In the model, patients begin treatment in one of three phases of CML: chronic phase, accelerated phase, or blast phase. Following initial treatment, patients enter one of three states, which are initial best response, no initial response or death. From these three states, patients either remain in their initial CML phase or death, or progress to a more advanced CML phase or death. The model assumes that patients can only progress to consecutive CML phases (from chronic to accelerated to blast to death) and cannot revert to an earlier phase of the disease. This is a limitation of the model, as it has been demonstrated, for example, that over 20% of patients in accelerated phase CML can return to the chronic phase with imatinib treatment[20].

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 received. This is another 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. 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 proportion of patients (assumed to be 8%).

2. Population

The model was designed to assess the cost-utility of dasatinib in adult patients with chronic, accelerated or blast phase CML resistant to imatinib used at daily doses of <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 51 years, as this was the reported median age of patients at the start of treatment in the non-comparative trial of dasatinib and imatinib (CA180-017)[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 of <600mg per day. A NICE technology appraisal of imatinib, issued in October 2003, recommended that patients who progressed from chronic phase CML whilst on treatment with imatinib should

continue imatinib treatment only as part of a research study[5]. No other recommendation was made by NICE for the management of such patients and, until the launch of dasatinib, the therapeutic options available for the treatment of such patients were limited to increasing the dose of imatinib, undergoing bone marrow transplantation (usually limited to use in younger patients with suitable donors) or trying another experimental therapy (see section 7.1, main document). Higher dose imatinib would therefore represent an appropriate comparator for dasatinib (but see section 9.1.1).

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 three sponsor clinical studies: in the chronic phase, three month data from study CA180-017 has been used; in the accelerated phase, six month data from study CA180-005 has been used; and for the blast phase, data from study CA180-006 has been used[2]. It is not immediately clear where 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 minor discrepancies compared with a range of other sources of the data. The probability of response with imatinib 400mg twice daily in the chronic phase is stated to have been derived from study CA180-017, but for the accelerated phase and the blast phase, two studies of imatinib have been cited[12,20] that again do not appear to accord with the figures used in the model. These two studies appear to have evaluated the efficacy of 400mg and 600mg daily doses of imatinib, rather than 400mg twice daily (although a minority of patients in the studies did use at least one dose of 400mg twice daily). 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 a range of published studies of imatinib. Disease progression is separated into short-term (4 to 12 months), and longer term (>12 months) periods. Long-term probabilities apply only to those patients who have not progressed within the first year. Where data are insufficient due to short follow-up times in these studies, the long- and short-term probabilities are assumed to be the same[2].

It is unclear how reliable this approach is, as it assumes that the rate of disease progression beyond the initial three months of treatment are independent of treatment received (i.e. the probability of progression is the same with dasatinib as with imatinib) and that, where long-term data are missing, the risk of disease progression is the same in patients who have progressed within the first year as in those who have not progressed within the first year. The results of these studies are based chiefly on imatinib doses of 400-600mg per day in patients who have failed treatment on interferon alfa. It is not clear how the estimates of probabilities of disease progression derived from these studies relate to the clinical situation being modelled currently. There also appears to be an erroneous probability of remaining in the accelerated phase of CML for patients who have a partial or complete cytogenetic response in the short-term period (4 to 12 months). Based on one of the imatinib studies[21], this probability is assumed to be 1.0000, which would imply that patients in the accelerated phase who experience a partial or complete cytogenetic

response would remain in the accelerated phase and cannot progress to more severe disease.

5.2. Utility values

The company submission states that, as no estimates of health utility in CML 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 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. 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 CML –related causes or non-CML-related causes. The probability of CML-related death is dependent upon patients' current health state and their response to treatment, as assumed from a published study of survival with imatinib treatment in patients with accelerated or blast phase CML[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.

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 CML treated with imatinib or dasatinib.

However, this utility weight associated with serious adverse events has not been specifically included in the analysis. No disutilities associated with any adverse events have been included in the base case analysis, but the one-way sensitivity analyses explore disutilities in the 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 desatanib[1].

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 derived for dasatinib from trials CA180-017 (chronic phase) and CA180-005 (accelerated and blast phases). For imatinib, the rates of adverse events were derived from trial CA180-017 (chronic phase) and assumed to apply to all phases. There appear to be some discrepancies in the rates of some adverse events listed in the company submission (and used in the model) and in the published paper for study CA180-017 (chronic phase). For example, the company submission does not report any serious (Grade 3-4) cases of neutropenia for dasatinib or imatinib in the chronic phase, and serious thrombocypoenia is reported as 22.8% versus 8.2%, respectively[2]. However, the published paper for this trial reports Grade 3-4 neutropenia to have occurred in 61% vs. 39% and Grade 3-4 thrombocytopenia to have occurred in 56% versus 14%, respectively[12]. The probabilities of adverse

events appear not to have been explored in sensitivity analyses, so the influence of these discrepancies on cost-effectiveness is uncertain.

6. Healthcare resource utilisation and cost

Resource use (excluding CML drug treatment costs) in the treatment of CML 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. These are 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 probabilities of some adverse effects (e.g. thrombocytopenia and neutropenia) used in the model[1] and those reported in the published paper[6]. 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 any 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% in the base case analysis, which is the preferred discount rate. Other discount rates were explored in sensitivity analyses.

8. Results

8.1. Base-case

The increment costs/QALY gained for treatment with dasatinib 70mg twice daily compared with imatinib 400mg twice daily starting in each phase of CML are presented in table one.

Table one. Incremental cost per QALYs for treatment with dasatinib (70mg twice daily) versus imatinib (400mg twice daily)

	CML phase		
	Chronic	**Accelerated**	**Blast**
Incremental costs	-£10,501	£98,550	£59,941
Incremental QALYs	0.64	2.21	0.92
ICER	**Dominant**	**£44,538**	**£63,817**
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 for treatment started in the chronic, accelerated and blast phases of CML. Probabilistic sensitivity analyses were also conducted.

9.1 One-way sensitivity analyses

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

9.1.1 Chronic phase CML

Varying the costs of resource use and the health state utilities by ±20%, and varying the time horizon, discount rates and disutility associated with side effects had little impact on the ICER. However, decreasing the daily dose of imatinib from 800mg to 600mg had a dramatic effect, moving dasatinib from being dominant over imatinib to having an ICER of £57,465 per QALY gained. This is an important finding as, according to the company submission, data from a survey of physicians (see section 3.5 of the budget impact analysis discussion) indicates that imatinib resistant patients receive, on average, 619mg daily in the chronic phase[1] (and not 800mg daily as modelled in the base case analysis).

9.1.2 Accelerated phase and blast phase CML

The estimated ICER in the accelerated and blast phases appeared to most sensitive to variation in the utilities associated with response to treatment in the accelerated and blast phases respectively, disutility associated with adverse events (but the range explored was 0.1 to 0.99, which are extremes), and the discount rates used. When costs were discounted at 6% and benefits at 1.5%, the ICER decreased substantially, but in none of the scenarios explored did the ICER decrease to ≤£30,000 per QALY gained.

9.2 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was conducted to account for parameter uncertainty – specifically in relation to certain costs, health state utilities, probabilities and mortality. The probabilities and costs of adverse events, and the daily dose of drugs appear not to have been explored in the probabilistic sensitivity analysis.

For the chronic phase of CML, the generated cost-effectiveness acceptability curve indicates the probability of dasatinib being cost saving is 60%. At a willingness to pay of £20,000 per QALY gained, the probability of dasatinib being cost-effective (compared with imatinib) is over 90%.

For the accelerated phase, dasatinib is not cost-effective below a willingness to pay of around £38,000 per QALY. To be cost-effective in 50% of cases, the willingness to pay would need to be around £45,000 per QALY gained and, for comparison with the chronic phase, to be cost-effective in over 90% of cases the willingness to pay would need to be around £47,000 per QALY gained.

For the blast phase, dasatinib is not cost-effective below a willingness to pay of around £48,000 per QALY gained. To be cost-effective in 50% of cases, the willingness to pay would need to be around £64,000 per QALY gained and, for comparison with the chronic phase, to be cost effective in over 90% of cases, the willingness to pay would need to be around £70,000 per QALY gained.

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 imatinib-resistant CML and in 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. 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].

3. Data sources

3.1. Incident cases

The company submission indicates that, based on data from the Welsh Cancer Surveillance and Intelligence Unit[22], 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[7]. The company submission states that 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 were 148 adults with CML in Wales in 2003. This is based on the application of the prevalence rate for England and Wales, as quoted in the NICE technology appraisal of imatinib[5], to the population of Wales. This figure of 148 adults has then been increased by 10% per year from 2003 to 2008 on the basis of data from Novartis which is reported to indicate the increased survival of patients following the introduction of imatinib[2]. This is not verifiable from the data and references provided. An increase of 10% each year in the prevalence of CML would increase the number of cases in 2003 from 148 to 256 in 2008. The company submission then adds 6 patients to this figure, although it is not clear why this has been done. The resultant figure of 262 patients with CML in Wales is then claimed to remain constant from 2008 to 2012. The company submission goes on to state that 251 patients would be treated for CML in Wales in 2008. No reference is provided to verify this, and there appears to then be an anomaly in the figure quoted for the number of cases that would be treated with imatinib in 2008, which is taken as 98% of 256 rather than 98% of 262.

The company submission estimates the number pf people likely to be prescribed dasatinib as 86 patients in 2008, rising to 88 patients in years 2009-12. This is based on the following calculations:

The company submission states that NICE estimates that 89% of patients are in the chronic phase, 6% in the accelerated phase and 5% in the blast phase[5]. On the basis of a published review of imatinib trial data and unpublished, company sponsored

physician survey data, the model assumes that 29% of patients in the chronic phase, 45% of patients in the accelerated phase and 92% of patients in the blast phase are resistant to imatinib treatment, and 1%, 2% and 5% of patients in each of the respective phases are intolerant to imatinib treatment. Therefore, 30% of patients in the chronic phase, 47% of patients in the accelerated phase and 97% of patients in the blast phase of CML would be eligible for dasatinib.

Applying these figures to the number of patients estimated to be treated with imatinib in 2008 (251 patients) would yield 67 patients with chronic phase CML, 7 patients with accelerated phase CML and 12 patients with blast phase CML, giving a total of 86 patients to be treated with dasatinib instead of imatinib. The corresponding figures for each year in the period 2009-12 are 68 patients, 7 patients and 13 patients, giving a total of 88 patients per year.

3.3. Market share

The company submission estimates the number pf people likely to be prescribed dasatinib as 86 patients in 2008, rising to 88 patients in years 2009-12. This is based on the following calculations:

The company submission states that NICE estimates that 89% of patients are in the chronic phase, 6% in the accelerated phase and 5% in the blast phase[5]. On the basis of a published review of imatinib trial data and unpublished, company sponsored physician survey data, the model assumes that 29% of patients in the chronic phase, 45% of patients in the accelerated phase and 92% of patients in the blast phase are resistant to imatinib treatment, and 1%, 2% and 5% of patients in each of the respective phases are intolerant to imatinib treatment. Therefore, 30% of patients in the chronic phase, 47% of patients in the accelerated phase and 97% of patients in the blast phase of CML would be eligible for dasatinib.

Applying these figures to the number of patients estimated to be treated with imatinib in 2008 (251 patients) would yield 67 patients with chronic phase CML, 7 patients with accelerated phase CML and 12 patients with blast phase CML, giving a total of 86 patients to be treated with dasatinib instead of imatinib. The corresponding figures for each year in the period 2009-12 are 68 patients, 7 patients and 13 patients, giving a total of 88 patients per year.

3.4. Rates of adoption

The model assumes that patients newly diagnosed with CML would be considered for BMT, 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.

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 (no further details provided). Well managed patients are assumed to receive imatinib 400mg once daily in the chronic phase and 600mg once daily in the accelerated and blast phases. Resistant patients are reported to receive higher doses, on average 619mg once daily in the chronic phase, 697mg in the accelerated phase and 721mg in the blast phase. Intolerant patients in any 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.

4. Results

4.1. Base-case

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 total cost of dasatinib is £2.74m in 2008, rising to £2.80m in each of years 2009-12. The incremental cost of using dasatinib instead of imatinib is estimated as approximately £96,000 in 2008 and £99,000 in each of years 2009-12.

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 incremental cost of dasatinib would be £48,000 in 2008, £74,000 in 2009 and £99,000 in 2010-12.

Appendix 3. Clinical Expert Summaries – supplied as a separate document

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

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