

Re-submission

[bosutinib 100mg, 500mg film-coated tablets \(Bosulif®\)](#) SMC No. (910/13) **Pfizer Ltd.**

09 January 2015

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a re-submission considered under the ultra-orphan medicine process

bosutinib (Bosulif®) is accepted for use within NHS Scotland.

Indication under review: Treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.

Major cytogenetic response was achieved in 23/52 patients who represented “unmet medical need” within a non-comparative phase I/II study, in which the full population included 546 patients with CP, AP or BP imatinib pre-treated Ph+ CML.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of bosutinib. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

Treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.

Dosing Information

Therapy should be initiated by a physician experienced in the diagnosis and the treatment of patients with CML.

The recommended dose is bosutinib 500mg orally once daily. In clinical trials, treatment with bosutinib continued until disease progression or until it was no longer tolerated by the patient.

The dose may be adjusted to bosutinib 600mg once daily in the following circumstances:

- Failure to achieve complete haematologic response by week 8
- Failure to achieve complete cytogenetic response by week 12

The summary of product characteristics (SPC) includes advice on dose adjustment in the event of adverse events.

Product availability date

27 March 2013

Bosutinib was designated as an orphan medicinal product for the treatment of CML on 12 February 2013. It also meets SMC ultra-orphan criteria.

Summary of evidence on comparative efficacy

Bosutinib is a second generation tyrosine kinase inhibitor (TKI) licensed for the treatment of CML, which is a haematopoietic stem cell disease characterised by a proliferation of granulocytes and their immature myeloid precursors including blast cells. CML has three phases: chronic phase (CP), accelerated phase (AP) and blast phase (BP), with the duration of untreated CP CML being three to five years. Current treatments include the first generation tyrosine kinase inhibitor, imatinib (commonly used first-line), and the second generation tyrosine kinase inhibitors, nilotinib and dasatinib.

A phase I/II, open-label, single arm, two-part study of bosutinib (study 200-WW) has been conducted in 571 patients with Ph+ leukaemia.^{1,3-9} Part 1 was a dose-escalation study to establish the maximum tolerated dose for use in part 2, and will not be discussed further. Part 2 studied the efficacy and safety of bosutinib in a partially heavily pre-treated population with more advanced disease stages. Patients aged ≥ 18 years with Ph+ CML or Ph+ acute lymphoblastic anaemia (ALL) who had failed imatinib (primarily refractory to full-dose imatinib [600mg], had disease progression/relapse while on full-dose imatinib, or were intolerant of any dose of imatinib) were recruited.⁶ In addition, patients were required to have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, and to have received no anti-

proliferative or anti-leukaemia treatment within seven days of bosutinib initiation. Stem cell transplantation was not permitted within the three months prior to study entry.^{4,7}

Patients were treated with oral bosutinib 500mg once daily which was continued until disease progression (transformation to AP/BP CML or loss of previously attained response), unacceptable toxicity or withdrawal of consent. A dose increase to bosutinib 600mg once daily was permitted for lack of efficacy, and if no bosutinib-related adverse event of at least grade 3 had occurred. The dose could be lowered in 100mg increments based on severity and duration of treatment-related toxicities and treatment was discontinued if 300mg/day was not tolerated.⁴

Efficacy was analysed in the following cohorts: CP CML (second-line; patients with imatinib resistance or imatinib intolerance and no previous TKI exposure other than imatinib [n=288]), CP CML (third-line; patients who had failed imatinib and dasatinib and/or nilotinib treatment [n=118]), AP CML (n=76) and BP CML (n=64).

The primary outcome was major cytogenetic response rate at 24 weeks analysed in the CP CML (second-line) cohort. Major cytogenetic response included partial plus complete cytogenetic responses and was defined as 0% to 35% Ph+ metaphases. It was achieved in 31% (90/288) of patients: imatinib resistant patients (33% [66/200]) and imatinib intolerant patients (27% [24/88]).⁸

Major cytogenetic response in the CP CML (third-line), AP CML and BP CML cohorts was analysed as a secondary endpoint. Additional secondary endpoints included duration of major cytogenetic response (Kaplan-Meier), complete haematological response (CHR), progression free survival (PFS) and overall survival (OS).⁸ A CHR responder had an improvement from baseline to achieve a confirmed CHR or maintenance of CHR with responses of at least four weeks duration with extramedullary involvement and peripheral blood and/or bone marrow documentation.⁸ PFS was defined as the time from first dose to disease progression as assessed by the investigator, treatment discontinuation due to death, or death within 30 days of last dose. OS was defined as the interval from the date of first dose to the date of death due to any cause.⁶

Results for the CP CML (third-line), AP CML and BP CML cohorts are presented in the table below from the most recent data snapshots. Results for the ALL cohort (n=24) and secondary endpoints for the CP CML (second-line) cohort are not reported as they are not relevant to the licensed indication.

Table: results of secondary endpoints in the relevant CML cohorts from study 200-WW 1,5,7-9

Chronic myelogenous leukaemia (CML) cohorts			
	Chronic phase CML (third-line) (n=118)*	Accelerated phase CML *** (n=76)	Blast phase CML *** (n=64)
Cumulative major cytogenetic response			
% (n/N); 95% CI	40% (44/110)** 95% CI not reported	35%; 24% to 47%	30%; 18% to 44%
Duration of major cytogenetic response			
K-M at 1 year %; 95% CI	74%; 57% to 85%	62%; 39% to 79%	7.9%; 0.5% to 30%
K-M at 2 years %; 95% CI	71%; 54% to 83%	<u>CiC</u>	<u>CiC</u>
K-M at 3 years %; 95% CI	64%; 46% to 78% **	NA	NA
Cumulative complete haematological response			
% (n/N); 95% CI	73% (85/116)** 95% CI not reported	35%; 24% to 47%	15%; 7.1% to 27%
Progression free survival			
Median	NR	22.1 months	5.5 months
% at 1 year; 95% CI	78%; 68% to 86%	65%; 52% to 75%	14%; 6.0% to 26%
% at 2 years; 95% CI	75%; 64% to 83%	<u>CiC</u>	<u>CiC</u>
Overall survival			
Median	NR	NR	11.1 months
% at 1 year; 95% CI	91%; 85% to 95%	76%; 65% to 84%	44%; 31% to 56%
% at 2 years; 95% CI	84%; 76% to 90%	<u>CiC</u>	<u>CiC</u>

*15 February 2012 snapshot unless indicated otherwise;**15 May 2013 snapshot; ***28 March 2011 snapshot.

CI=confidence interval, K-M=Kaplan Meier, NA=not assessed, NR=not reached

The EQ-5D is a 5-item validated assessment instrument consisting of five items: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, where each item is scored from 1 (“no problems”) to 3 (“extreme problems”). The EQ-5D was measured at weeks 4, 8 and 12, then every 12 weeks and at treatment completion. The mean utility at baseline was maintained throughout the study for the CP CML (third-line), AP CML and BP CML cohorts.¹⁰

The EMA considered that a subgroup of the pivotal study could support a last line indication and requested a post hoc analysis of a subgroup of patients who were classed as having “unmet medical need” in CP or AP/BP CML. A total of 52 patients were selected who had presence of a breakpoint cluster region-Abelson (BCR-ABL) kinase domain mutation that would be reasonably expected to confer resistance to dasatinib (F317, E255) or nilotinib (E255, Y253, F359) and a medical history or evidence of prior TKI intolerance (to nilotinib and dasatinib). A major cytogenetic response was achieved in 9 of 21 patients with CP CML (failure with two TKIs); duration of response was 8 to 204 weeks with a treatment duration of 35 to >215 weeks. A major cytogenetic response was achieved in 9 of 15 patients with CP CML (failure with

imatinib); duration of response was 12 to 155 weeks with a treatment duration of 24 to >197 weeks. In addition three of five patients with AP CML, and two of eleven patients with BP CML achieved a major cytogenetic response.^{1,3}

Other data were also assessed but remain commercially confidential.*

Summary of evidence on comparative safety

Discontinuation due to adverse events occurred in around 21% of patients in the CP CML (second-line) and CP CML (third-line) cohorts. Diarrhoea (any grade) was the commonest adverse event reported (in over 80% of patients) and was primarily managed with anti-diarrhoeal medication, treatment interruption or treatment reduction. Grade 3/4 diarrhoea was reported in around 9% of patients. Other adverse events reported included upper abdominal pain, fatigue, pyrexia, rash, headache, cough, pruritis and arthralgia. Grade 3/4 laboratory abnormalities included thrombocytopenia, neutropenia, lymphopenia, anaemia, leukopenia, hypermagnesaemia, elevated alanine transaminase, elevated lipase and hypocalcaemia.^{1,9}

In the “unmet medical need” post hoc subgroup (28 March 2011 snapshot), all patients reported at least one adverse event and 69% (36/52) of patients reported an adverse event of grade 3/4. The proportion of patients who had a treatment-emergent adverse event that led to discontinuation was 25% (13/52). Serious adverse events were reported in 54% (28/52) of patients.¹

Summary of clinical effectiveness issues

CML is a haematopoietic stem cell disease characterised by a proliferation of granulocytes and their immature myeloid precursors including blast cells. Reciprocal translocation of the long arms of chromosome 9 and chromosome 22 (known as Philadelphia chromosome [Ph] and present in 95% of CML) results in a characteristic cytogenetic abnormality. CML, if untreated, progresses from the chronic phase (CP) and accelerated phase (AP) and into the blast phase (BP) with the duration of untreated CP CML being three to five years. Current treatments include the first generation TKI, imatinib (commonly used first-line), and the second generation TKIs, nilotinib and dasatinib. Between 17% to 25% of patients will fail or become intolerant to imatinib within five years of treatment and some patients will also develop resistance, due to genetic mutations, or intolerance to second line treatments. Bosutinib is a second generation TKI and has been designated an orphan product for the treatment of CML by the European Medicines Agency (EMA).¹⁻³

There are few treatment options for adult CML patients when imatinib, nilotinib and dasatinib are not considered appropriate whether through resistance, intolerance or co-morbidities. While cure of CML is achieved with haematopoietic stem cell transplantation, this is usually performed in paediatric and younger adult patients and is associated with significant morbidity and mortality.¹ Other treatments include interferon alfa and best supportive care comprising palliative chemotherapy (hydroxycarbamide). Clinical experts consulted by SMC considered there is currently unmet need in treatment of CML after other TKIs, due to a lack of treatment options in patients not suitable for haematopoietic stem cell transplantation. Bosutinib meets SMC ultra-orphan criteria and has been designated an orphan medicine by the EMA.

Following a review of the clinical trial programme for bosutinib, the EMA considered that only a last-line indication for patients with CML with “unmet medical need” could be considered for bosutinib as efficacy in first-line use was not robust and there are no relevant comparative data required for approval of second-line use. Therefore, a post-hoc defined subgroup (“unmet medical need”), that included 52 patients from the pivotal study, was selected for analysis. The EMA commented that although the “unmet medical need” subgroup was small, data from the larger subgroups of the study also provided evidence of efficacy. The EMA also noted that the favourable durability of response in the CP CML (third-line) cohort was of importance in terms of minimising the risk of transformation from CP to AP/BP CML. Conditional marketing authorisation was granted and the company is to conduct a single arm open-label multi-centre efficacy and safety study in the population described within the licensed indication by September 2018.¹

To provide data to support the economic evaluation, the submitting company has proposed that a ‘proxy’ population derived from the CP CML (third-line), AP and BP CML cohorts of the pivotal study might represent the patients that would be treated in clinical practice. A cumulative major cytogenetic response was achieved/maintained in 40% of patients with CP CML treated with bosutinib third line and in lower proportions of patients with AP (35%) and BP CML (30%). However these cohorts do not strictly reflect the population eligible for treatment with bosutinib within its licensed indication.

There are no comparative data for bosutinib. The submitting company considered best supportive care to be the relevant comparator and proposed that hydroxycarbamide be a proxy for it. The company noted that as the pivotal bosutinib study and comparator studies were of single-arm, non-comparative design, only a naïve indirect comparison was possible. Two hydroxycarbamide studies in CP CML were identified.^{11,12} One study was conducted in patients who had failed imatinib treatment and included 61 patients who received treatments other than stem-cell transplant or 2nd-generation TKIs (including 12 patients treated with hydroxycarbamide).¹¹ Estimated survival was 77% and 70% at two and three years, respectively. The second study presented data for hydroxycarbamide following failure of interferon.¹² The relevance of this study, in terms of hydroxycarbamide use after TKI treatment, is limited. No studies of hydroxycarbamide in advanced CML were identified. Therefore, due to limited efficacy data for hydroxycarbamide, the comparative efficacy of bosutinib versus best supportive care is uncertain.

As well as hydroxycarbamide (as a palliative treatment), clinical experts consulted by SMC reported the use of stem cell transplantation and interferon alfa. The submitting company excluded these as comparators as they considered that patients eligible for stem-cell transplant would have already received this, and because of lack of data for interferon in refractory patients treated with TKIs.

Bosutinib would provide patients previously treated with one or more TKI(s) (and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options), with a third-line treatment option. Adverse event rates with bosutinib were high, with hepatotoxicity (raised transaminases), gastrointestinal events (mainly diarrhoea) and cardiac arrhythmias being the most important toxicities.¹

Summary of patient and clinician engagement

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of bosutinib, as an ultra orphan medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Most patients with chronic myelogenous leukaemia (CML) are treated effectively with available tyrosine kinase inhibitors but for a small number of patients where these are not effective, not tolerated or contra-indicated due to pre-existing medical conditions, there are currently very limited options. Having access to bosutinib with a different side effect profile is a key advantage.
- This will be a valuable but only occasionally used medicine in NHS Scotland for a small number of patients (suggested <10 per annum) to optimise life expectancy and quality of life.
- The medicine restores independence with a steady accrual of self worth and dignity.
- Bosutinib is an oral agent taken at home, once daily with food and as such it provides a 'convenient' mode of administration with a reduced need for hospital attendance for administration.
- SMC has already accepted imatinib and nilotinib for CML treatment and the view expressed was that this 'minority group within a minority group of patients', that may benefit from bosutinib, should have access to a third line option on equity grounds with the aim of achieving a therapeutic outcome.
- The PACE group noted an equity issue that can be distressing for patients if unable to access bosutinib.

Summary of ultra orphan decision-making framework

Bosutinib has been considered by SMC using its decision-making framework for the assessment of ultra-orphan medicines. Relevant factors under each of the criteria are summarised below:

Nature of the condition

With the advent of TKIs, treatment of CML has changed greatly and CML is now generally managed as a long term condition. However, if left untreated or if TKIs fail, patients with CML will progress through symptoms that gradually increase in severity. Chronic phase patients would likely transform to the more aggressive accelerated phase and blast crisis.

A diagnosis of CML can be particularly devastating for patients and their families because patients are often asymptomatic at the point of diagnosis. Patients are usually below retirement

age at diagnosis and often live with a fear of disclosure of their condition to employers and the wider family because of the lay view that a “leukaemia” diagnosis equates to a death sentence.

Impact of the new technology

Most CML patients are treated effectively with available TKIs, but for a small number of patients where these are not effective, not tolerated or contraindicated due to pre-existing medical conditions, there are currently very limited treatment options. Bosutinib would offer patients with CML an additional third- line treatment option.

As noted above, efficacy data were available from a post hoc analysis of a subgroup of patients in the pivotal study who were classed as having “unmet medical need” in CP or AP/BP CML. Direct comparative data against best supportive care were not available but within the economic analysis, the company undertook modelling and predicted survival gains of approximately 3 years in the chronic and accelerated phases and 1.2 years in blast crisis.

The side effect profile of bosutinib is different to other TKIs and, of note, the cardiac and pulmonary adverse effects seen with other medicines are not a concern. Intolerance is the main problem with TKIs, thus having access to a medicine with a different side effect profile is a key advantage.

Value for money

The submitting company presented a cost-utility analysis comparing bosutinib to hydroxycarbamide in adult patients with CP, AP and BP Ph+ CML, previously treated with one or more TKI(s), and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options. The comparator selected was hydroxycarbamide as a proxy for best supportive care.

The submission included three separate Markov models designed to capture patients in the CP, AP and BP of CML. A lifetime horizon was used for each model. The CP model included five health states: CP on treatment, CP off treatment, AP, BP and death with patients starting in the CP on treatment health state. The AP model included four health states (AP on treatment, AP off treatment, BP and death) and the BP model used three health states (BP on treatment, BP off treatment and death). In all models, patients were assumed to receive hydroxycarbamide after discontinuing bosutinib. Once on hydroxycarbamide, patients in the CP model would then spend a fixed duration of time in the AP and BP health states, while patients in the AP model would spend a fixed time in the BP state.

For the bosutinib arm of the CP model, data from the third-line cohort from the pivotal study were used. The submitting company indicated that this cohort was expected to be the most representative of patients who would be unsuitable for nilotinib, dasatinib and imatinib and therefore receive bosutinib in practice. In the bosutinib arm of the AP and BP models, the full AP and BP cohorts from the pivotal study were used. Overall survival in the CP, AP and BP models was calculated through extrapolation and fitting parametric curves directly to the pivotal study data from the data snapshot 15 February 2012. However as overall survival for the CP cohort is high, there was uncertainty around the survival estimate and an alternative cumulative survival approach was also provided in the base case in the CP analysis; as such, results are reported for the ‘extrapolated’ model and the ‘cumulative survival model’. Under the latter approach, OS was estimated as the sum of time on bosutinib treatment plus the anticipated OS benefit associated with best supportive care (hydroxycarbamide); this does not assume any benefit beyond the treatment period. For the hydroxycarbamide arm of the CP model, data from the National Institute for Health and Care Excellence (NICE) technology appraisal (TA) 241

were used which reported 3.5 years overall survival for patients treated with hydroxycarbamide at third-line.¹³ For the hydroxycarbamide arms of the AP model, in the absence of any direct evidence on the survival of patients, it was assumed that the mean survival was equal to the time spent in the AP phase and BP from the CP model. This equated to a mean survival of 16 months (10 months in the AP and 6 months BP) to which an exponential curve has been fitted. The survival estimate for the hydroxycarbamide patients in the BP model had been assumed to be 6 months.

The company selected the utility values from EQ-5D data collected in the pivotal study for the base case analysis. Utilities for bosutinib on treatment were taken from week 24 in the CP model, week 12 in the AP model and week 8 in the BP model. These time points were selected because over half of patients were still on treatment increasing the reliability of the utility estimates. The submitting company indicated that these utility estimates should also have taken into account disutility arising from adverse events and no further adjustment was made.

Medicines costs for bosutinib in the base case were calculated at a dose 500mg/day and the time on treatment was taken from data from study 200-WW from the most recent data cut at 15 May 2013. Resource use was included according to phase of CML and included outpatient appointments, inpatient stays and intensive care unit stays. The frequency of resource use was based on the estimates used in a NICE TA 251 where estimates were taken from a UK survey and then adjusted based on expert opinion.²

A patient access scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group as acceptable for implementation in NHS Scotland. Under the PAS, a confidential discount is offered on the list price of the drug. With the PAS, the results were as follows:

Bosutinib versus hydroxycarbamide	Incremental cost	Incremental quality adjusted life years (QALYs)	Incremental cost-effectiveness ratio (ICER)
Chronic Phase CML Model			
Extrapolation	£148,130	3.79	£39,119
Cumulative	£95,240	2.05	£46,410
Accelerated Phase CML Model			
Extrapolation	£126,158	2.01	£62,619
Blast Phase CML Model			
Extrapolation	£51,788	0.85	£61,270

A range of one-way sensitivity analyses on selected parameters was provided for each phase of the model. In the CP extrapolation analysis, the results were most upwardly sensitive to assuming bosutinib is used until transformation (£45,816 with PAS) or assuming OS for hydroxycarbamide was 5 years (£48,426 with PAS). If shorter time horizons of two or five years were used, the with-PAS ICER rose to £141,756 and £68,540 respectively. The use of alternative extrapolation approaches did not increase the ICERs as the base case selected the most conservative form. For the CP model using the cumulative survival approach, the results were much less sensitive and the highest ICER was £47,821 when an alternative treatment duration was used. Probabilistic sensitivity analysis indicated that in the CP phase model using

the cumulative survival approach, there would be approximately 50%, 80% and 90% chance of cost effectiveness at willingness to pay levels of £40k, £50k and £60k respectively.

For the AP model, the ICER was most sensitive to the shortening of the time horizon to 2 years (£96,649 with PAS) or assuming treatment until transformation (£75,834 with PAS). In the BP phase, the results were sensitive to estimating OS using the cumulative survival approach (£81,049 with PAS) or assuming the time in BP was 13 months (£87,852 with PAS).

The base case cost per QALY results for all three groups are relatively high and, in addition, there are a number of weaknesses:

- The company has adopted survival estimation approaches in this resubmission which are more conservative and thus welcomed, but as with all economic models which require extrapolation, there remains some uncertainty as to the true level of incremental benefit. The cumulative survival approach produced a more conservative ICER in the CP model, which the New Drugs Committee (NDC) felt may be appropriate, as it did not assume continuing benefits beyond treatment. However, this modeling approach led to ICERs which were relatively insensitive to change in efficacy or treatment duration. This was a concern as there may be some remaining uncertainty which hasn't been captured in sensitivity analysis. This is because people who take hydroxycarbamide earlier in the treatment pathway may be expected to have a greater life expectancy than those at the point of bosutinib treatment discontinuation but the model assumed the same level of effect. The company did provide some supplementary analysis to reduce the survival benefit for hydroxycarbamide used post-bosutinib and this gave ICERs of £48k to £62k when the survival gain was varied between 40 and 30 months respectively.
- As noted above, there are weaknesses with the clinical data and this impacts upon the robustness of the outcomes in the economic model. The clinical data used in the analysis were based on the third-line cohort from the pivotal study, rather than the 'unmet need' subgroup that the EMA considered to be most relevant for the indication under review. The company justified the use of the third-line cohort on the basis that the sample size is larger and therefore uncertainty is reduced. The submitting company also stated that as the response rates in the unmet need subgroup were consistent or more favourable, the results presented above may be considered conservative.
- Hydroxycarbamide has been used as the comparator in the analysis, and while NDC accepted this as a valid, it is noted that other treatments may be used in some patients.

Patient and Clinician Engagement

A Patient and Clinician Engagement (PACE) meeting was held for this submission. Participants at the meeting indicated a range of potential impacts of the new technology for the patient and families/ carers.

Impact beyond direct health benefits and on specialist services

At the PACE meeting, participants felt that bosutinib offers the best option for this very small group of patients to optimise life expectancy and quality of life. Participants stated that tolerable adverse effects and the convenience of taking an oral preparation at home would enable patients to keep going with day to day activities such as work, caring for children and grandchildren or education. Patients stated that treatment can maintain independence, self care and dignity. It was reported that this is key to the psychological health of these patients and their families as their condition no longer dominates their whole life. With reduced need for support, patients could remain in their own homes. Better symptom control e.g. in terms of pain

and tiredness was said to lead to psychological benefits for the patient and the whole family as can the reassurance that a third-line treatment is available.

Equity issues were raised both at the PACE meeting and by the submitting company. Patients indicated that availability of bosutinib would provide fair access to a treatment option for patients for whom, through no fault of their own, other treatment is not effective, not tolerated or contra-indicated. The company highlighted that only a few patients are eligible for stem cell transplant and thus bosutinib offered these patients access to an additional therapy option; this was noted as being particularly relevant for patients from ethnic minority groups where there is a challenge regarding availability of matched donors.

Costs to the NHS and Personal Social Services

The submitting company has estimated that between 8 and 11 patients would be treated with bosutinib each year and that this would be associated with a net medicines budget impact of £275k to £371k per year before any patient access scheme discounts were applied. The submitting company did not estimate any costs outside of the NHS.

The committee also considered the benefits of bosutinib in the context of the SMC decision modifiers and agreed that criteria were satisfied for a substantial improvement in quality of life and the absence of other treatments of proven benefit. In addition, as bosutinib is an ultra orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, and application of the appropriate SMC modifiers, the Committee accepted bosutinib for use in NHS Scotland.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

The following information reflects the views of the specified Patient Groups.

- Submissions were received from Leukaemia CARE and the Chronic Myeloid Leukaemia Support Group (CMLSG), which are both registered charities.
- Both charities have received funding from several pharmaceutical companies over the past two years, including from the submitting company.
- Chronic myeloid leukaemia is a type of blood cancer, which can have debilitating systems including: fatigue, loss of appetite, weight loss, increased nocturnal sweating and unusual bruising or bleeding. More advanced symptoms can include anaemia, bone pain, fevers and repeated infections. Due to the often gradual onset of symptom diagnosis can come as a complete shock. Many feel isolated due to the small numbers affected by this condition.
- The majority of patients will respond to first or second-line treatments and go on to have a relatively normal life expectancy. However, there is a need for additional treatments for those who are intolerant or unsuitable for current TKI treatments.

- The main advantage of bosutinib is that it is the only realistic treatment option for those intolerant or resistant to first and second line TKI's. Without this treatment this small group has little realistic expectation of long term survival.

Additional information: guidelines and protocols

NICE published TA 241; Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) (part review of NICE technology appraisal guidance 70), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance, in January 2012.¹³ It includes the following recommendations:

- Nilotinib is recommended for the treatment of CP or AP Ph+ CML in adults:
 - whose CML is resistant to treatment with standard-dose imatinib or
 - who have imatinib intolerance and
 - if the manufacturer makes nilotinib available with the discount agreed as part of the patient access scheme.
- Dasatinib is not recommended for the treatment of CP, AP or BP CML in adults with imatinib intolerance or whose CML is resistant to treatment with standard-dose imatinib.
- High-dose imatinib (600mg or 800mg in CP, 800mg in AP or BP) is not recommended for the treatment of CP, AP or BP Ph+ CML that is resistant to standard-dose imatinib.

European Society for Medical Oncology (ESMO) published Chronic myeloid leukemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up, in 2012.¹⁴ It includes the following treatment choices:

Chronic phase

- First-line: Imatinib 400mg, or nilotinib 600mg, or dasatinib 100mg
- Second-line:
 - In case of intolerance, switch to another, taking into consideration the side effects of the first tyrosine kinase inhibitor, and comorbidities
 - In case of failure of imatinib, switch to nilotinib, or dasatinib, taking into consideration the presence and the type of BCR-ABL KD mutation
 - In case of failure of nilotinib or dasatinib, switch to dasatinib or nilotinib, taking into consideration the presence and the type of BCR-ABL KD mutation. Consider an allogeneic haematopoietic stem cell transplantation (alloHSCT)
- Third-line
 - In case of failure of two or three tyrosine kinase inhibitors, consider alloHSCT

Accelerated/blast phase

- Tyrosine kinase inhibitor naïve
 - Imatinib 600 or 800mg, or nilotinib 800mg or dasatinib 140mg, and consider alloHSCT
- Tyrosine kinase inhibitor pre-treated
 - Switch to another tyrosine kinase inhibitor, consider chemotherapy and alloHSCT

European LeukemiaNet (ELN) published ELN recommendations for the management of chronic myeloid leukaemia, in 2013.¹⁵

These guidelines were produced by an ELN expert panel who reviewed prior and new studies, to update recommendations made in 2009.

Chronic phase

- First-line (outside of clinical trials): imatinib (400mg once daily), nilotinib (300mg twice daily), or dasatinib (100mg once daily).
- Second line, intolerance to the first tyrosine kinase inhibitor: Imatinib, nilotinib or dasatinib
- Second line, failure of imatinib first line: Dasatinib, or nilotinib, or bosutinib, or ponatinib.
- Second line, failure of nilotinib first line: Dasatinib, or bosutinib, or ponatinib.
- Second line, failure of dasatinib first line: Nilotinib, or bosutinib, or ponatinib.
- Third line, failure of, or/and intolerance to, two tyrosine kinase inhibitors: Any one of the remaining tyrosine kinase inhibitors.
- In patients with T315I mutation, treatment options include ponatinib or alloHSCT.
- In patients with failure of second-generation tyrosine kinase inhibitors, alloHSCT can be considered as a second or third-line treatment option.

Additional information: comparators

Hydroxycarbamide (considered palliative treatment), interferon alfa (CP CML only) or alloHSCT.

Cost of relevant comparators

Drug	Dose Regimen	Cost for 28 days (£)
bosutinib	500mg orally once daily	3,437
hydroxycarbamide	20 to 30mg/kg orally once daily	9 to 12
interferon alfa 2a (Roferon®)	Subcutaneously on days 1 to 3; 3 million IU daily, days 4 to 6; 6 million IU per day, days 7 to 84; 9 million IU units per day	1,064 to 1,192
interferon alfa 2b (IntronA®)	Subcutaneously, 4 to 5 million IU/m ² daily (monotherapy)	840 to 1,048

Doses are for general comparison and do not imply therapeutic equivalence. Costs are from MIMs and eVadis on 24 September 2014. Cost based on body weight of 70kg or body surface area of 1.8m² where relevant. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there to be 8 patients eligible for treatment with bosutinib in year 1, rising to 11 patients in year 5. Treatment uptake was estimated at 100% per year and, assuming some treatment discontinuation, it was estimated that 6 patients would be treated in year 1, rising to 8 patients in year 5.

Without PAS

The company estimated the gross drug budget impact to be £276k in year 1, rising to £372k in year 5. The net drug budget impact was estimated to be £275k in year 1, rising to £371k in year 5.

Other data were also assessed but remain commercially confidential.*

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

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12. Ibrahim AR, Clark RE, Holyoake TL, et al. Second-generation tyrosine kinase inhibitors improve the survival of patients with chronic myeloid leukemia in whom imatinib therapy has failed. *Haematologica* 2011;96:1779-82.
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14. Baccarani M, Pileri S, Steegmann JL, et al. Chronic myeloid leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23 Suppl 7:vii72-7
15. Baccarani M, Deininger M, Rosti G et al. European leukemianet recommendations for the management of chronic myeloid leukemia. Blood. 2013.122:872-884.

This assessment is based on data submitted by the applicant company up to and including 14 November 2014.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*

http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.