Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Professor Jonathan G Fox

# Re-submission

## dasatinib 20mg, 50mg, 80mg, 100mg and 140mg film-coated tablets (Sprycel®)

SMC No. (370/07)

## Bristol-Myers Squibb Pharmaceuticals Ltd.

05 August 2016

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 NHS Scotland. The advice is summarised as follows:

**ADVICE**: following a re-submission assessed under the orphan process

**dasatinib (Sprycel®)** is accepted for use within NHS Scotland.

**Indication under review:** for the treatment of adult patients with chronic, accelerated or blast phase chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib mesilate.

In patients with chronic, accelerated or blast phase CML, dasatinib produced haematological and cytogenetic responses in two phase III dosing ranging studies. In a phase II study dasatinib was associated with higher haematological and cytogenetic responses relative to another tyrosine kinase inhibitor in patients with chronic phase CML.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of dasatinib. This advice is contingent upon the continuing availability of the PAS 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**

Published 12 September 2016

## Indication

For the treatment of adult patients with chronic, accelerated or blast phase chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib mesilate.

## Dosing Information

The recommended starting dose is 100mg once daily for chronic phase and 140mg once daily for accelerated, myeloid or lymphoid blast phase (advanced phase) CML, administered orally.

In clinical studies dose escalation to 140mg once daily (chronic phase CML) or 180mg once daily (advanced phase CML) was allowed in patients who did not achieve a haematologic or cytogenetic response at the recommended starting dose. Dose modifications should be considered for the management of treatment toxicity.

In clinical studies, treatment with dasatinib was continued until disease progression or until no longer tolerated by the patient. The effect of stopping treatment on long-term disease outcome after the achievement of a cytogenetic or molecular response [including complete cytogenetic response (CCyR), major molecular response (MMR) and complete molecular response [MR4.5: decrease of 4.5 log below the standard baseline]) has not been investigated.

Dasatinib must not be crushed or cut in order to minimize the risk of dermal exposure, it must be swallowed whole. Tablets can be taken with or without a meal and should be taken consistently either in the morning or in the evening.

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

## Product availability date

November 2006
Dasatinib meets SMC orphan criteria.

## Summary of evidence on comparative efficacy

Chronic myelogenous leukaemia (CML) is characterised by a proliferation of granulocytes in blood and bone marrow. It progresses through a chronic phase (CP), which may last several years, to an accelerated phase (AP) and then a blast phase (BP) which has a very poor prognosis. Ninety-five percent of people with CML have a chromosomal abnormality resulting in an oncogene called the 'Philadelphia chromosome' or BCR-ABL. This gene codes for proteins with high tyrosine phosphokinase activity. Dasatinib, a second generation tyrosine kinase inhibitor (TKI), is a competitive inhibitor at the binding site for BCR-ABL kinase (or other protein kinases) and prevents activation or over-expression of pathways responsible for malignant cells.[1-3]

Dasatinib has previously been reviewed by SMC in April 2007 and was accepted for restricted use in patients with CP CML. At that time, the submitting company presented the clinical evidence that supported the initial marketing authorisation: five phase II, open-label, clinical studies, including a 12-week interim analysis of the START-R study. The SMC advice was subsequently superseded by a National Institute of Health and Care Excellence (NICE) multiple technology appraisal (MTA) in January 2012 (TA241) which did not recommend dasatinib.[1] Healthcare Improvement Scotland has advised that this guidance is valid for Scotland [4]

In this resubmission, the submitting company has presented evidence published since the initial SMC appraisal: two phase III, randomised, open-label, multicentre dasatinib dose-ranging studies (CA180-034 and CA180-035) and longer term follow up of the phase II START-R study.

CA180-034 was a two by two factorial design dasatinib dose ranging study designed to compare two total daily doses (140mg versus 100mg) and two dosing regimens (once daily versus twice daily) in 670 adults with CP Philadelphia positive (Ph+) or BCR-ABL gene positive CML who were resistant or intolerant to imatinib. Patients were stratified according to imatinib status (resistant or intolerant) then randomised equally to one of four dasatinib treatment groups: 100mg once daily, 50mg twice daily, 140mg once daily or 70mg twice daily. Dose modification was permitted in patients with an inadequate response or drug related toxicity (total daily dose [TDD] 20mg to 180mg daily). Treatment continued until disease progression or intolerable toxicity as determined by the treating physician.[5-7]

The primary outcome was the rate of major cytogenetic response (MCyR) in patients with imatinib-resistant disease with a minimum of six months follow up. MCyR included patients with complete (0% Ph+ cells in metaphase in bone marrow) or partial (>0% to 35% Ph+ cells in metaphase in bone marrow) cytogenetic responses. The primary objective of the study was achieved; patients with imatinib-resistant disease allocated to once daily therapy achieved a MCyR (52%) that was non-inferior to the twice daily schedule (49%), treatment difference 2.8% (95% confidence interval [CI]: -6.0% to 12%). The 100mg TDD group (50%) was also non-inferior to the 140mg TDD group (51%) in patients with imatinib-resistant disease, measured by MCyR; treatment difference -0.8% (95% CI: -9.6% to 8.0%).[5]

In all patients (imatinib resistant and imatinib intolerant), at a minimum of six months follow-up, MCyR was observed in 59%, 54%, 56% and 55% of patients in the 100mg once daily, 50mg twice daily, 140mg once daily and 70mg twice daily groups respectively, with 95% CI overlapping for all treatment groups. Imatinib-intolerant patients (n=498) consistently showed a higher response rate compared to those resistant to imatinib (n=172) (74%, 73%, 70% and 68% versus 53%, 47%, 50% and 51% in respective groups).[5] At two-year follow up, MCyR was observed in 63%, 61%, 63% and 61% of patients respectively. Response was complete in 50%, 50%, 50% and 54% of the respective groups.[8] There were a number of secondary outcomes measuring haematological and cytogenetic response and longer term follow-up (up to seven years) measuring molecular response, progression-free survival and overall survival that supported the primary outcome, suggesting no efficacy differences between the different dosing levels and dosing schedules.[5, 7-9]

CA180-035 was a dose comparison study in adults with AP (n=317) and BP (n=210) CML and Ph+ acute lymphoblastic leukaemia (n=84) who were resistant or intolerant to imatinib. Patients were stratified by type of disease, CML phase and imatinib status (resistant or intolerant) then randomised equally to receive dasatinib 140mg once daily or 70mg twice daily. Dose modification was permitted in patients with an inadequate response or drug related toxicity (TDD 80mg to 180mg daily).[10,11] Since this resubmission only relates to patients with CML, results in patients with Ph+ acute lymphoblastic leukaemia are not presented.

The primary outcome for the study overall was the rate of major haematological response (MaHR) in all randomised patients at six months. Sub-group analyses were carried out by disease type. MaHR was defined as complete haematological response (CHR) or no evidence of leukaemia (NEL).[13]

In the subgroup of patients with AP CML, at 15 months follow up, MaHR was observed in 66% (105/158) and 68% (108/159) of patients in the dasatinib 140mg once daily and 70mg twice daily groups respectively. In the once daily group, MaHR was 63% (74/117) in imatinib-resistant patients and 76% (31/41) in those with imatinib intolerance. In the twice daily group, MaHR was 68% (79/116) in imatinib-resistant patients and 67% (29/43) in those with imatinib intolerance.[10] In the subgroup of

patients with myeloid BP CML, MaHR at two years was 28% in both the dasatinib 140mg once daily (21/75) and dasatinib 70mg twice daily (21/74) groups. In patients with lymphoid BP CML, MaHR at two years was 42% (14/33) and 32% (9/28) in the respective dosing groups.[11]

Secondary outcomes assessed haematological and cytogenetic response, progression-free survival and overall survival, and results supported the primary outcome.

START-R was a phase II, multicentre, open-label study conducted in 150 adults with CP CML who had failed treatment with imatinib 400mg or 600mg per day. Patients were stratified by study site and cytogenetic response on imatinib (response or no response) then randomised in a 2:1 ratio to receive dasatinib 70mg twice daily (original licensed dose) or high-dose imatinib (400mg twice daily).[14] Dasatinib dose modification was permitted for lack of response or toxicity (TDD 80mg to 180mg). The imatinib dose could be reduced to 600mg for toxicity. Treatment continued until disease progression, unacceptable toxicity or patient withdrawal. Patients could cross treatment arms on progression or intolerable toxicity and in the imatinib group patients could cross to dasatinib if a MCyR or a ≥30% metaphase reduction by 12 weeks was not achieved.[14]

The primary outcome was the MCyR rate at 12 weeks. The study was not designed to compare groups, which was performed as a post hoc analysis. MCyR was defined as ≤35% of Ph+ cells.[14] MCyR at 12 weeks was 36% and 29% in the dasatinib and imatinib groups, respectively.[14] Based on the Kaplan-Meier estimates, the proportion of patients who maintained MCyR for one year was approximately 92% of dasatinib-treated patients and 74% of imatinib-treated patients. At 24 months follow up, progression free survival, defined as time from randomisation to disease progression, crossover due to progression, or death was 86% and 65% in the dasatinib and imatinib groups, respectively.

At the two-year follow-up, the MCyR rate was 49% (19/39) in patients who crossed over from imatinib to dasatinib and 15% (3/20) in patients who crossed over from dasatinib to imatinib.[2,14]

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

## Summary of evidence on comparative safety

The dose ranging studies CA180-034 and CA180-035 provide evidence that the current once daily dosing schedule for dasatinib has improved tolerability over the previously licensed twice daily dosing schedule, mainly due to the reduced occurrence of pleural effusion.[8] The START-R study only included the previously licensed dosing schedule for dasatinib so does not provide any comparative safety data for the relevant dosing schedule.

There are no direct comparative safety data for dasatinib at the licensed dosing schedule. A retrospective review of the medical records of 105 patients attending one of five Polish tertiary care haematological centres who started either dasatinib (n=50) or nilotinib (n=55) as second-line treatment of CP CML between January 2007 and December 2012 has been conducted. It provides a real world comparison of severe vascular events and other non-haematological complications of the two treatments. Patients were observed for a median of 28 months (range 1 to 93). Pleural effusion was reported more commonly in patients receiving dasatinib (26% versus 2%, p=0.003) and severe vascular events, including peripheral artery occlusive disease, were reported more commonly by patients receiving nilotinib (11% versus 4%, p=0.16).[15]

## Summary of clinical effectiveness issues

Allogeneic stem cell transplant is a potentially curative treatment option for patients with CML however the need for a suitable donor and the procedure related morbidity and mortality excludes this as a treatment option for many. TKIs are therefore the mainstay of treatment for CML. Dasatinib is a second generation TKI and has been designated an orphan medicine for the treatment of CML by the European Medicines Agency (EMA) and meets SMC orphan criteria.[2, 16]

NICE TA241 assessed the use of dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant CML, and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance. The committee considered that dasatinib and nilotinib were similar. Nilotinib was considered a cost-effective use of NHS resources when a patient access scheme (PAS) was applied, dasatinib was not recommended by NICE due to higher cost since a PAS was not available for dasatinib at that time. High-dose imatinib was considered more expensive and less effective than nilotinib so was not recommended for use.[1] Healthcare Improvement Scotland has advised that this guidance is valid for Scotland.[4]

SMC has also accepted bosutinib and ponatinib for use in patients with CP, AP or BP CML according to their marketing authorisations. Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, in particular for disease mutations that may be more sensitive to dasatinib than the other TKIs and for patients unsuitable for other TKIs due to co-morbidities or adverse effects. [1]

The mean terminal half life of dasatinib is approximately five to six hours[3] and a twice daily dosing schedule was originally licensed.[5] However, since the two phase III studies demonstrated that the once daily dosing schedules were equally effective and potentially better tolerated than the twice daily dosing schedules, and these are now the licensed doses.

The studies presented were open-label, the primary outcomes were surrogate markers and there was a high degree of crossover in all studies. The proportion of patients with BP disease was small, especially lymphoid BP so the estimates of effect size may be imprecise. There are no data comparing the dasatinib once daily licensed dosing schedule to any comparator. The START-R study provides evidence for dasatinib twice daily relative to high dose imatinib; however, imatinib was not accepted for use by NICE TA241.[1]

As there is no direct evidence comparing dasatinib to the relevant comparators (nilotinib, bosutinib and ponatinib), the company presented a systematic literature review to identify published evidence for treatments in the second-line setting (defined as TKI relapsed/refractory/resistant or TKI intolerant) for patients with CP, AP or BP CML. The purpose was to inform a network meta-analysis (NMA); however, this was not possible, mainly due to a lack of control arms for studies assessing nilotinib, ponatinib and bosutinib. The company therefore presented the baseline characteristics and efficacy outcomes from relevant clinical studies of dasatinib, nilotinib, bosutinib, ponatinib and high dose imatinib to allow a naive indirect comparison. Most patients were receiving second-line treatment although some studies included patients at later lines of therapy. In addition there was heterogeneity across the studies with regards to duration of CML disease and response at study entry. Nilotinib and dasatinib were considered to be broadly similar and the limited evidence versus bosutinib and ponatinib did not suggest any important differences. Due to variation in the design of the BP CML studies and small patient numbers, it was difficult to compare these. Safety outcomes were not presented.

The availability of dasatinib would provide another oral treatment option with a different adverse event profile to currently available therapies. Clinical experts consulted by SMC clinical considered that the place in therapy for dasatinib would be as a treatment option for patients with certain co-morbidities, e.g. those with cardiovascular risk factors. The adverse event profile for dasatinib is well characterised. Dasatinib can be taken with or without food, compared to nilotinib where patients are required to avoid food two hours before and one hour after each twice daily dose.[17]

## Summary of Patient and Clinical Engagement (PACE)

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

The key points expressed by the group were:

- CML is a rare type of leukaemia and diagnosis can be devastating for patients and their families. Symptoms can vary with the stage of the disease, and include fatigue, pain, frequent infections, abdominal discomfort and fever.
- An allogeneic stem cell transplant (ASCT) can be potentially curative but is not an option for many CML patients and carries relatively high morbidity and mortality.
- TKI treatment can fail due to resistance or intolerance. Second line choice is often nilotinib but this may not be suitable in patients with pre-existing conditions/co-morbidities, which is not usually a concern with dasatinib. Nilotinib also has dosing restrictions that can impact on normal life.
- Dasatinib is an oral treatment and has no dietary restrictions. This can allow patients to return to work and a more normal life. Some disease mutations may be more sensitive to dasatinib than other TKI's. Dasatinib is thought to be more effective at crossing the blood-brain barrier than other TKI's so can be more effective when CNS disease is present.
- Adverse effects of dasatinib were not considered a concern. Increased risk of pleural effusion was discussed but is easily medically managed and very few patients stop treatment as a result.
- The PACE group was of the view that dasatinib should be made available in NHS Scotland in line with the licensed indication. Dasatinib can allow patients to participate fully in family life and has advantages over other TKI treatments such as nilotinib with regards to its administration and in patients with cardiac and metabolic syndromes

**Additional Patient and Carer Involvement**

We received patient group submissions from Leukaemia Care and the Chronic Myeloid Leukaemia Support Group (CMLSG). Leukaemia Care has received <10% pharmaceutical company funding in the past two years, including from the submitting company. CMLSG has received 95% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from each patient group also participated in the PACE meeting. The keys points of their submissions have been included in the full PACE statement.

## Summary of comparative health economic evidence

The submitting company provided a cost-utility analysis which compared dasatinib against nilotinib, imatinib 600mg once daily, imatinib 400mg twice daily, bosutinib and ponatinib in adult patients with CP, AP or BP CML with resistance or intolerance to prior therapy. Patients who received dasatinib in CP were treated with the 100mg once daily dose and patients in AP or BP received the 140mg once

daily dose. The company considered nilotinib to be the primary comparator and the base case analysis assumed patients had received first-line treatment with imatinib.

A time-in-state model with a 40 year time horizon was used to assess the cost-effectiveness of dasatinib versus the comparators. In terms of model structure, for patients initiated in CP and AP, the model consisted of three health states: pre progression, post-progression and death. For patients who were initiated in BP, a post-progression state was not modeled and patients could either remain in BP or transition to death. Prior to progression or death, patients could receive a second-line, third-line, or final line of therapy, while patients in the post-progression state were assumed to receive final line therapies.

The sources of the clinical data included the CA180034 and CA180035 studies, which were used to model PFS and OS curves for the following response categories: complete response, partial response and failure. Separate PFS curves were estimated for patients initiated to treatment in CP and AP and separate OS curves were estimated for patients initiated to treatment in CP, AP and BP. The PFS and OS curves were also independent of treatment. Key variables in the economic model included response rates, which determined the PFS or OS curve the patient would follow. The response rates for each comparator were derived from a naïve indirect comparison and separate rates were presented for each phase of the disease. In addition, response rates were presented for the overall population under review as well as resistant or intolerant to imatinib sub-populations. Adverse event data, response related discontinuation rates, and non-response discontinuation rates were taken from sources identified in a systematic literature review, relevant guidelines and clinical studies.

Utility estimates for the CP, CP post progression, AP, BP, were taken from a published study. Utilities were also presented separately for responders and non-responders within each health state.

Medicines costs were included in the analysis as well as costs associated with background resource use, post-progression therapies, palliative care and adverse events.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a discount was offered on the list price of the medicine. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented, and a summary of the ranges of figures in the various populations is noted below. PAS are in place for nilotinib and bosutinib and these were included in the analysis by using an estimate of the relevant price for nilotinib and bosutinib.

Without the dasatanib PAS, in the overall population, the cost-effectiveness results ranged from dasatanib being the dominant treatment (cheaper and more effective) in the case of CP patients versus nilotinib, bosutinib and ponatanib and in AP patients versus ponatanib to a cost per QALY of £241,742 versus imatinib 600mg in the myeloid BP population. In a few scenarios, dasatanib was found to be cheaper but less effective than the comparator therapies (ie versus bosutinib in the AP and BP populations). In the imatinib resistant population, the results ranged from dasatanib being the dominant treatment in the case of CP patients versus nilotinib, bosutinib and ponatanib and in AP patients versus ponatanib to a cost per QALY of £881,782 versus imatinib 600mg in the myeloid BP population. In a few scenarios, dasatanib was found to be cheaper but less effective than the comparator therapies (ie versus bosutinib in the AP and BP populations). In the imatinib intolerant population, the results ranged from a finding of dominance versus bosutinib and ponatanib in the CP population to dasatanib being dominated (more expensive, less effective) versus ponatanib in the myeloid BP group. Dasatanib was also found to be cheaper but less effective in the myeloid BP group versus bosutinib.

The company also provided a cost-minimisation analysis. However, as noted above, owing to commercial in confidence considerations, SMC is unable to publish these results. It is noted that with the PAS, dasatanib became a cost-effective treatment option.

The main weaknesses were:

- The economic analysis was based on a naive indirect comparison which was associated with limitations such as heterogeneity between data sources. Despite these weaknesses and the uncertainty associated with a naive comparison, the company concluded that dasatinib may be similar to nilotinib, bosutinib and ponatinib. It is also worth noting that NICE TA241 reported that dasatinib and nilotinib were similar in terms of efficacy, as there was little evidence to distinguish between the two. However, the results of the economic evaluation generated a QALY and a life year gain for dasatinib versus the comparators in some cases, which suggested benefit attributable to dasatinib that may not be supported by the conclusion of the naive indirect comparison.

- The company response suggested that the QALYs gains were relatively small when compared to the absolute or total QALYs. Given the conclusion of similar efficacy between dasatinib and nilotinib, bosutinib and ponatinib, the cost-minimisation analysis was considered the more relevant format for the economic analysis.

- SMC clinical experts also noted differences in adverse events between the medicines and therefore the company has provided cost-minimisation analyses with differences in adverse events included which generally suggested that dasatinib was a cost-effective treatment option. However, it should be noted that these analyses are also limited by the use of naive adverse event data.

The Committee considered the benefits of dasatinib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as dasatanib is an orphan medicine, SMC can accept greater uncertainty in the economic case.

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

## Additional information: guidelines and protocols

NICE technology appraisal 241; Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant 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 (January 2012). It includes the following recommendations:

- Nilotinib is recommended for the treatment of chronic or accelerated phase Philadelphia-chromosome-positive 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 chronic, accelerated or blast-crisis phase CML in adults with imatinib intolerance or whose CML is resistant to treatment with standard-dose imatinib.
- High-dose imatinib is not recommended for the treatment of chronic, accelerated or blast-crisis phase Philadelphia-chromosome-positive CML that is resistant to standard-dose imatinib.

Updated European LeukemiaNet recommendations were published in 2013. Second or subsequent line of treatment for CP CML can be any of the three TKIs at either the standard dose (imatinib 400mg once daily, dasatinib 100mg once daily or nilotinib 300mg twice daily) or higher dose (imatinib 400mg twice daily, nilotinib 400mg twice daily or dasatinib 70mg twice daily or 140mg once daily). Bosutinib and ponatinib have also been approved for patients resistant or intolerant to prior therapy. Busulfan is not recommended and hydroxycarbamide should only be used until diagnosis is confirmed. Interferon alfa is only suitable in the unusual situation when a TKI cannot be used. In patients who progress from CP CML to AP or BP CML who have received a TKI, then a TKI that has not previously been used should be considered. Ponatinib is suitable for patients with T3151 mutation. Patients with AP or BP CML should be considered for an allogeneic stem cell transplant.

## Additional information: comparators

Nilotinib, bosutinib and ponatinib.

## Cost of relevant comparators

| Drug | Dose Regimen | Cost per 28 days (£) |
|---|---|---|
| **Dasatinib** | **Orally 100mg to 140mg once daily (chronic phase CML) or 140mg to 180mg once daily (accelerated, myeloid or lymphoid blast phase CML)** | **2,338 to 3,507** |
| Ponatinib | Orally, 45mg once daily | 4,713 |
| Bosutinib | Orally, 500mg once daily | 3,437 |
| Nilotinib | Orally, 400mg twice daily | 2,433 |

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis and BNF online on 06/05/2016. Costs of bosutinib and nilotinib are based on continuation of recommended starting doses. Costs do not take any patient access schemes into consideration.

## Additional information: budget impact

The submitting company estimated there would be would be 196 patients eligible for treatment with dasatinib in year 1 and 231 patients in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

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

References

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


1. National Institute for Health and Care Excellence (NICE). Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML). TA 241. 2012.
2. European Medicines Agency (EMA). European Public Assessment Report Marketing Variation. Dasatinib (Sprycel®). 03/08/2008, EMEA/H/C/709/II/08. www.ema.europa.eu.
3. Dasatinib tablets (Sprycel®) Summary of product characteristics. Bristol-Myers Squibb Pharmaceuticals Ltd. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 27/03/16.
4. Healthcare Improvement S. NICE (Multiple) Technology Appraisal Guidance No 241. NICE technology appraisal guidance 70 part review: Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML). 2012 [cited; Available from: http://www.healthcareimprovementscotland.org/programmes/nice_guidance_and_scotland/mta_resources/apprasial_241.aspx.
5. Shah NP, Kantarjian HM, Kim DW, Rea D, Dorlhiac-Llacer PE, Milone JH, *et al.* Intermittent target inhibition with dasatinib 100 mg once daily preserves efficacy and improves tolerability in imatinib-resistant and -intolerant chronic-phase chronic myeloid leukemia. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2008;26(19):3204-12. Epub 2008/06/11.
6. Chronic Myelogenous Leukemia (CML) - Follow on: Study of BMS-354825 in Subjects With CML. NCT00123474. Available from: https://clinicaltrials.gov [cited 25 April 2016].
7. Shah NP, Guilhot F, Cortes JE, Schiffer CA, le Coutre P, Brummendorf TH, *et al.* Long-term outcome with dasatinib after imatinib failure in chronic-phase chronic myeloid leukemia: follow-up of a phase 3 study. Blood. 2014;123:2317-24. Epub 02/27.
8. Shah NP, Kim DW, Kantarjian H, Rousselot P, Llacer PE, Enrico A, *et al.* Potent, transient inhibition of BCR-ABL with dasatinib 100 mg daily achieves rapid and durable cytogenetic responses and high transformation-free survival rates in chronic phase chronic myeloid leukemia patients with resistance, suboptimal response or intolerance to imatinib. Haematologica. 2010;95:232-40. Epub 02/09.
9. Shah NP RP, Schiffer CA, et al. Seven-Year (yr) Follow-up of Patients (pts) with Imatinib-Resistant or -Intolerant Chronic-Phase Chronic Myeloid Leukemia (CML-CP) Receiving Dasatinib in Study CA180-034, Final Study Results. 56th ASH Annual Meeting and Exposition; San Francisco, CA December 6-9 2014. Session 632 Abstract 520. 2014.
10. Kantarjian H, Cortes J, Kim DW, Dorlhiac-Llacer P, Pasquini R, DiPersio J, *et al.* Phase 3 study of dasatinib 140 mg once daily versus 70 mg twice daily in patients with chronic myeloid leukemia in accelerated phase resistant or intolerant to imatinib: 15-month median follow-up. Blood. 2009;113:6322-9. Epub 04/17.
11. Saglio G, Hochhaus A, Goh YT, Masszi T, Pasquini R, Maloisel F, *et al.* Dasatinib in imatinib-resistant or imatinib-intolerant chronic myeloid leukemia in blast phase after 2 years of follow-up in a phase 3 study: efficacy and tolerability of 140 milligrams once daily and 70 milligrams twice daily. Cancer. 2010;116:3852-61. Epub 06/22.
12. **Commercial in Confidence*
13. Advanced Chronic Myelogenous Leukemia (CML) - Follow On: Study of BMS-354825 in Subjects With CML. NCT00123487. Available from: https://clinicaltrials.gov [cited 25 April 2016].
14. Kantarjian H, Pasquini R, Levy V, Jootar S, Holowiecki J, Hamerschlak N, *et al.* Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia resistant to imatinib at a dose of 400 to 600 milligrams daily: two-year follow-up of a randomized phase 2 study (START-R). Cancer. 2009;115:4136-47. Epub 06/19.
15. Gora-Tybor J, Medras E, Calbecka M, Kolkowska-Lesniak A, Ponikowska-Szyba E, Robak T, *et al.* Real-life comparison of severe vascular events and other non-hematological complications in

patients with chronic myeloid leukemia undergoing second-line nilotinib or dasatinib treatment. Leukemia & lymphoma. 2015;56:2309-14. Epub 01/08.
16. Baccarani M, Deininger MW, Rosti G, Hochhaus A, Soverini S, Apperley JF*, et al.* European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood. 2013;122:872-84. Epub 06/28.
17. Nilotinib capsules (Tasigna®) Summary of Product Characteristics. Novartis Pharmaceuticals, U. K. Ltd. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 29/10/2015

This assessment is based on data submitted by the applicant company up to and including 16 May 2016.

**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.*