

**AWMSG Secretariat Assessment Report – Limited submission****Dasatinib (Sprycel®) 20 mg, 50 mg, 70 mg, 80 mg, 100 mg and 140 mg film-coated tablets**

**Company:** Bristol-Myers Squibb Pharmaceuticals Ltd

**Licensed indication under consideration:** For the treatment of paediatric patients weighing  $\geq 10$  kg with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in chronic phase (Ph+CML-CP) or Ph+CML-CP resistant or intolerant to prior therapy including imatinib

**Date of licence extension:** 2 July 2018

**Comparator(s)**

The comparators included in the company submission are:

- Imatinib for newly diagnosed Ph+CML-CP
- Nilotinib for Ph+CML-CP in patients who are resistant or intolerant to imatinib

**Limited submission details**

The limited submission criteria were met based on a minor licence extension and an anticipated usage in NHS Wales considered to be of minimal budgetary impact.

**Clinical effectiveness**

- Dasatinib has previously been recommended by the National Institute for Health and Care Excellence for the treatment of newly diagnosed Ph+CML-CP in adults (TA426) and Ph+CML-CP in adult patients who are resistant or intolerant to imatinib (TA425). Dasatinib is available in NHS Wales for adults under a Department of Health Patient Access Scheme (PAS).
- This submission covers the licence extension to include paediatric patients weighing  $\geq 10$  kg with newly diagnosed Ph+CML-CP, or with Ph+CML-CP resistant or intolerant to prior therapy including imatinib.
- The comparators included in the submission have not been appraised by the All Wales Medicines Strategy Group (AWMSG) for the indication under consideration. Imatinib was licensed for the treatment of adult and paediatric patients with newly diagnosed and previously treated Ph+CML in 2002 and 2001, respectively. AWMSG issued a Statement of Advice for nilotinib for the treatment of paediatric patients with newly diagnosed Ph+CML-CP and Ph+CML-CP with resistance or intolerance to prior therapy including imatinib in June 2018. Imatinib is recommended in the 2014 British guidelines as the tyrosine kinase inhibitor of choice for the first-line treatment of CML in paediatric patients. At the time the British guidelines were published nilotinib, another tyrosine kinase inhibitor, did not have a licence for use in children and no recommendation is included for its use in this population.



- The company submission includes results from a phase II, open-label, non-randomised, multicentre study (CA180-226) to assess the clinical efficacy and safety of dasatinib in paediatric patients with Ph+CML-CP.
- Study CA180-226 included three cohorts; only two are relevant to this submission. Patients in Cohort 1 had Ph+CML-CP and were resistant or intolerant to imatinib, and patients in Cohort 3 had newly diagnosed Ph+CML-CP. Patients in Cohort 1 received dasatinib tablets (n = 29) whilst patients in Cohort 3 were split into two groups: one received tablets (n = 51) and the other received the powder for oral suspension formulation with the option to switch to tablets after 12 months of treatment (n = 33). The applicant company has not included the powder for oral suspension in their submission. In Cohort 1 the primary outcome was major cytogenetic response (MCyR) rate and in Cohort 3 it was complete cytogenetic response (CCyR) rate. Response rates > 30% and > 55%, respectively, were considered of clinical interest.
- Results showed that in Cohort 1, the cumulative MCyR rate was 89.7% at 12 months (95% confidence interval [CI]: 72.6 to 97.8) and the median time to MCyR was 3.1 months (95% CI: 2.8 to 4.1). In Cohort 3, the cumulative CCyR rate at 12 months was 92.9% (95% CI: 85.1 to 97.3) and the median time to CCyR was 5.6 months (95% CI: 3.3 to 5.8). These results are broadly in line with those obtained from adult studies (CA180-034 and CA180-056) and in some cases better. However, due to disease differences between adult and paediatric CML patients it may not be appropriate to compare directly.
- Secondary outcomes for both cohorts included progression-free survival (PFS) and overall survival (OS). Estimated PFS at 48 months was 78% and 93% in Cohort 1 and 3, respectively. Estimated OS at 48 months was 96% for Cohort 1 and there were no deaths reported for patients in Cohort 3 at the time of data collection.
- The European Medicines Agency (EMA) considers the open, non-comparative design of the study acceptable when taking into account the low incidence of CML in the paediatric age group, that the medicine is approved and well-studied in adults in the same indication, and the endpoints used in study CA180-226.
- Pooled data (n = 188) from study CA180-226 and a phase I study showed that 83.0% of paediatric patients experienced a drug-related adverse event whilst on dasatinib and 18.6% of patients experienced a serious drug-related adverse event. The overall safety profile of dasatinib in the paediatric population was, however, similar to that of the adult population, with the exception of no reported pericardial effusion, pleural effusion, pulmonary oedema, or pulmonary hypertension in the paediatric population. The discontinuation rate was also low and, with the exception of haematologic adverse events, most adverse events were grade 1 or 2. Drug-related adverse events associated with bone growth and development were reported after at least 2 years of treatment; however, the results are difficult to interpret and require long-term follow-up.
- This submission only covers the tablet formulation. The administration of tablets to children can be difficult, especially in the case of dasatinib where the licence does not allow for the tablets to be crushed or dispersed. Until the powder for oral suspension becomes available not all patients eligible under the licence may be able to receive treatment with dasatinib. The EMA notes in their assessment that the powder for oral suspension formulation fulfilled an unmet need.

## Budget impact

- The company has calculated the budget impact separately for the imatinib resistant/intolerant and newly diagnosed patient populations, and based their estimates for Wales on UK data from the Office of National Statistics and the Decision Resourcing Group.
- The company estimates that dasatinib will partially displace imatinib in newly diagnosed patients with Ph+CML-CP. Based on the company market share estimates, assuming uptake of 50% in Year 1 and Year 5, the number of patients eligible for treatment with dasatinib is 1 in Year 1 and Year 5. The net medicine acquisition cost of treating newly diagnosed patients with dasatinib (based on the PAS price) is [commercial in confidence data removed] in Year 1 and Year 5.
- Based on the company market share estimates, assuming 100% uptake in Year 1 to Year 5 (minus 1% mortality), one imatinib resistant/intolerant patient is eligible for treatment with dasatinib in Year 1 and in Year 5. Assuming displacement of nilotinib (list price) results in cost savings of [commercial in confidence data removed] in Year 1 and in Year 5. Alternatively, when assuming that dasatinib will displace standard of care (no treatment), the net medicine acquisition costs of treating imatinib resistant/intolerant patients (based on the PAS price) are [commercial in confidence data removed] in Year 1 and Year 5.
- Nilotinib is available in NHS Wales for adults under a Department of Health PAS. The company conducted sensitivity analyses with discounts for nilotinib ranging from 5% to 95%. Applying a 5% discount results in a cost saving of [commercial in confidence data removed] in Year 1 and in Year 5. Applying a 95% discount results in a net medicine acquisition cost of [commercial in confidence data removed] in Year 1 and Year 5.
- Clinical expert opinion sought by AWTTTC suggests that nilotinib is used infrequently in paediatric patients with Ph+CML-CP resistant or intolerant to imatinib.
- Due to the low number of eligible patients, the number of patients receiving the new medicine, allowing for discontinuations, have been rounded.

## Consideration of All Wales Medicines Strategy Group (AWMSG) policy relating to orphan and ultra-orphan medicines and medicines developed specifically for rare diseases

- Dasatinib (Sprycel<sup>®</sup>) does not have EMA designated orphan status. The applicant company suggests that the prevalence of the population for the full licensed indication of dasatinib meets the AWMSG policy relating to orphan and ultra-orphan medicines and medicines developed specifically for rare diseases. Based on the Decision Resourcing Group mature market data the prevalence of CML in the UK is estimated at 6,375 cases. Dasatinib (Sprycel<sup>®</sup>) is also licensed for Ph+ acute lymphoblastic leukaemia (ALL). The prevalence of ALL in the UK is estimated at 6,574. Based on CML and ALL prevalence estimates, the applicant company estimates that the total number of patients eligible for treatment with dasatinib in Wales is 338–340. The All Wales Therapeutics and Toxicology Centre (AWTTTC) considers dasatinib to be eligible to be appraised as a medicine developed specifically to treat rare diseases as the full population of the licensed indication does not exceed the orphan threshold of  $\leq 5$  in 10,000 persons [ $\leq 1,500$  patients in Wales]). The New Medicines Group (NMG) and AWMSG will consider additional criteria (see Table 1) if they consider dasatinib (Sprycel<sup>®</sup>) meets the criteria to be appraised in line with the AWMSG orphan, ultra-orphan and medicines developed specifically for rare diseases policy.

**Table 1. Evidence considered by NMG/AWMSG**

| NMG/AWMSG Considerations  | AWTTC Comments   |
|---|--|
| The degree of severity of the disease as presently managed, in terms of survival and quality of life impacts on patients and their carers   | There is a scarcity of data relating to survival outcomes in paediatric CML, no UK-specific data and survival is dependent upon a number of factors. However, it is recognised that survival has improved since the introduction of the tyrosine kinase inhibitors (TKI), the first being imatinib. Post-TKI data from one non-UK observational study estimates a five-year overall survival of 94% for patients aged 8 months to 18 years. Post-TKI data (retrospective) for US patients aged 15 to 44 years estimates five-year overall survival of 86% and 95%. QoL in cancer patients is expectedly poor. In childhood cancer, factors affecting patient QoL, additional to the stresses and effects from disease treatment, include parental psychological distress, and children newly diagnosed with cancer and who are undergoing treatment have been found to have impaired health-related QoL. |
| Whether the medicine addresses an unmet need (e.g. no other licensed medicines)   | Nilotinib and imatinib are already licensed. Nilotinib is licensed for paediatric patients with Ph+CML-CP with resistance or intolerance to prior therapy including imatinib, and adult and paediatric patients with newly diagnosed Ph+CML-CP. Imatinib is licensed for adult and paediatric patients with Ph+CML-CP after failure of interferon-alpha therapy, and for adult and paediatric patients with newly diagnosed Ph+CML for whom bone marrow transplantation is not considered as the first line of treatment.  |
| Whether the medicine can reverse or cure, rather than stabilise the condition   | Dasatinib does not reverse or cure Ph+CML-CP.  |
| Whether the medicine may bridge a gap to a “definitive” therapy (e.g. gene therapy) and that this “definitive” therapy is currently in development  | The company states that dasatinib can be a bridge to a stem cell transplant in paediatric patients who are not well controlled. This is supported by AWTTC sought clinical expert opinion.   |
| The innovative nature of the medicine   | Dasatinib is not considered innovative. It is a second generation TKI; nilotinib is another second generation TKI which is already licensed.   |
| Added value to the patient (e.g. impact on quality of life such as ability to work or continue in education/function, symptoms such as fatigue, pain, psychological distress, convenience of treatment, ability to maintain independence and dignity)   | Dasatinib is an effective and well tolerated treatment which enables children with CML to lead a “normal life” and improves their quality of life.   |
| Added value to the patient’s family (e.g. impact on a carer or family life)   | Disease management of CML is associated with high burden of lay care which impacts upon the carer (mostly parents) and the family of the paediatric patient. An effective treatment will allow family members and carers to resume daily activities and therefore additional benefits from a societal perspective are anticipated.   |
| AWMSG: All Wales Medicines Strategy Group; AWTTC: All Wales Therapeutics and Toxicology Centre; CML: chronic myelogenous leukaemia; NMG: New Medicines Group; Ph+CML-CP: Philadelphia chromosome positive chronic myelogenous leukaemia in chronic phase; QoL: Quality of Life; TKI: tyrosine kinase inhibitor. |  |

| <b>Additional information</b>  |
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| <ul style="list-style-type: none"> <li>• AWTTC is of the opinion that, if recommended, dasatinib (Sprycel®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.</li> </ul> |

- The company does not anticipate that dasatinib (Sprycel®) will be supplied by a home healthcare provider.

### Evidence search

**Date of evidence search:** 20 November 2018.

**Date of range of evidence search:** No date limits were applied to database searches.

### Further information

This assessment report will be considered for review every three years.

References are available on request. Please email AWTTTC at [AWTTTC@Wales.nhs.uk](mailto:AWTTTC@Wales.nhs.uk) for further information.

This report should be cited as: All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Dasatinib (Sprycel®) 20 mg, 50 mg, 70 mg, 80 mg, 100 mg and 140 mg film-coated tablets. Reference number: 1514. February 2019.