

# Office of Clinical Pharmacology

NDA Number	NDA 021986
Link to EDR	<a href="\\cdsesub1\evsprod\NDA021986\0161">\\cdsesub1\evsprod\NDA021986\0161</a>
Applicant	Bristol-Myers Squibb Company
Submission Date	6/29/2018
Submission Type	Efficacy supplement
Brand Name	SPRYCEL®
Generic Name	Dasatinib
Dosage Form and Strength	Tablets: 20 mg, 50 mg, 70 mg, 80 mg, 100 mg, and 140 mg.
Route of Administration	Oral
Approved Indications	<ul style="list-style-type: none"> <li>Newly diagnosed adults with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase.</li> <li>Adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib.</li> <li>Adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy.</li> <li>Pediatric patients with Ph+ CML in chronic phase</li> </ul>
Approved Dosing Regimens	<ul style="list-style-type: none"> <li>Chronic phase CML in adults: 100 mg once daily.</li> <li>Accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL in adults: 140 mg once daily.</li> <li>Chronic phase CML in pediatrics: starting dose based on body weight.</li> <li>Administer orally, with or without a meal. Do not crush, cut, or chew tablets.</li> </ul>
Applicant Proposed Indication	<ul style="list-style-type: none"> <li>Pediatric patients with newly diagnosed Ph+ ALL in combination with chemotherapy</li> </ul>
Applicant Proposed Dosing Regimen	<ul style="list-style-type: none"> <li>Chronic phase ALL in pediatrics: starting dose based on body weight.</li> </ul>
OCP Division	Division of Clinical Pharmacology V (DCPV)
OND Division	Division of Hematology Products (DHP)
OCP Primary Reviewer	Liang Li, Ph.D.

OCP Team Leader	Ruby Leong, Pharm.D.
OCP Final Signatory	Nam Atiqur Rahman, Ph.D.

## EXECUTIVE SUMMARY

SPRYCEL® (dasatinib), an inhibitor of kinases (e.g., BCR-ABL, SRC family, c-KIT, EPHA2, and PDGFRβ), received FDA approval for adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy including imatinib in 2006, newly diagnosed adults with Philadelphia chromosome-positive (Ph+) CML in chronic phase and adults with Ph+ acute lymphoblastic leukemia (ALL) with resistance or intolerance to prior therapy in 2010, and pediatric patients with Ph+ CML in chronic phase in 2017.

In the current efficacy supplement, the Applicant submitted results from two trials for pediatric exclusivity determination (Written Request [WR] Amendment 5 issued on June 21, 2018; Reference ID: 4281468). The Applicant proposes SPRYCEL for the treatment of pediatric patients with newly diagnosed Ph+ ALL in combination with chemotherapy at the same starting dose based on body weight (Table 1) as approved for pediatric patients with Ph+ CML in chronic phase.

Table 1: Dosage of SPRYCEL for Pediatric Patients

Body Weight (kg) <sup>a</sup>	Daily Dose (mg)
10 to less than 20	40 mg
20 to less than 30	60 mg
30 to less than 45	70 mg
at least 45	100 mg

<sup>a</sup> Tablet dosing is not recommended for patients weighing less than 10 kg.

The recommended dose should be administered orally once daily with or without food. Recalculate the dose every 3 months based on changes in body weight, or more often if necessary. Do not crush, cut or chew tablets. Swallow tablets whole.

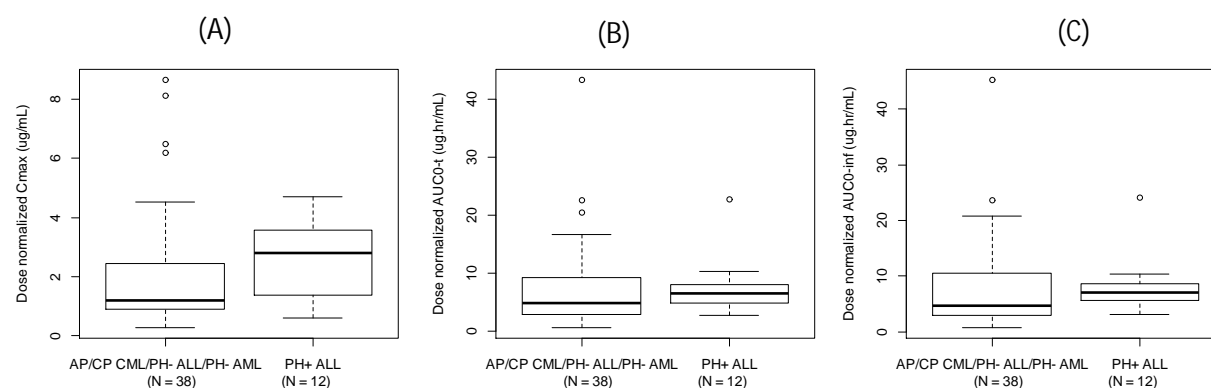
To support the registration of the newly proposed patient population, the Applicant submitted efficacy and safety data from two clinical trials:

Registrational Trial CA180372: An open-label, multi-center, historically-controlled trial to evaluate safety and efficacy of dasatinib at a daily dose of 60 mg/m<sup>2</sup> for up to 24 months plus chemotherapy compared to historical data for chemotherapy alone and imatinib plus chemotherapy in pediatric patients aged 1 to <18 years.

Supportive Trial CA180204: A Phase 2, open-label, multi-center, single-arm study in children and young adults (1 to ≤30 years) with newly diagnosed Ph+ ALL.

The 3-year binary event-free survival (EFS) for patients in Trial CA180372 was 65.9% (95% CI 54.5, 76.0). In general, adverse reactions reported in the two pediatric trials were consistent with the known safety profile of SPRYCEL in adults and expected effects of chemotherapy. There was no pharmacokinetic (PK) data obtained from the two trials. Based on the limited PK data from previously submitted dose-escalation pediatric Trial CA180018, the dose-normalized  $C_{max}$  (Figure 1A),  $AUC_{0-t}$  (Figure 1B) and  $AUC_{0-inf}$  (Figure 1C) of dasatinib were generally comparable in pediatric patients with Ph+ ALL (N = 12) and in pediatric patients with acute phase (AP) or chronic phase (CP) CML, Ph- ALL or Ph- AML (N = 38).

Figure 1: Dose-Normalized Exposure of Dasatinib in Pediatric Patients with Ph+ ALL and in Pediatric Patients with AP/CP CML, Ph- ALL or Ph- AML from Trial CA180018



The Office of Clinical Pharmacology has reviewed the information contained in this efficacy supplement. There are additional administration considerations for pediatric patients who have difficulty swallowing tablets whole. Five patients with Ph+ ALL 2 to 10 years of age received at least one dose of SPRYCEL tablet dissolved in lemonade or preservative free juice in Trial CA180372. Although efficacy and safety results were consistent with those observed with the intact tablets, the previously submitted relative bioavailability Trial CA180352 indicated that exposure was reduced by 16% for tablets dissolved in orange juice as compared to intact tablets. Therefore, the following language is recommended in the labeling:

#### Section 8.4 Pediatric Use

##### Pediatric Patients with Difficulty Swallowing Tablets

Five patients with Ph+ ALL 2 to 10 years of age received at least one dose of SPRYCEL tablet dissolved in lemonade or preservative-free juice on Study CA180372. The bioavailability of dissolved tablets was 16% lower than that of intact tablets [see *Clinical Pharmacology (12.3)*]. Given the lower exposure of dissolved tablets and limited data from Study CA180372, it is unclear if efficacy and safety would be altered by dissolving SPRYCEL tablets [see *Dosage and Administration (2.2)*].

#### Section 12.3 Pharmacokinetics

When administered to adult healthy subjects as dissolved tablets in juice, the adjusted geometric mean ratio was 0.97 (90% CI: 0.85, 1.10) for  $C_{max}$  and 0.84 (90% CI: 0.78, 0.91) for AUC as compared to intact tablets.

## RECOMMENDATION

This NDA efficacy supplement is approvable, fulfills the clinical pharmacology components of the WR, and there is no post-marketing requirement (PMR) or commitment (PMC) from a clinical pharmacology perspective.

### Signatures:

---

Liang Li, Ph.D.

Reviewer

Division of Clinical Pharmacology V

---

Ruby Leong, Pharm.D.

Team Leader

Division of Clinical Pharmacology V

---

Nam Atiqur Rahman, Ph.D.

Division Director

Division of Clinical Pharmacology V

Cc: OHOP: RPM - W Lee; MTL - D Przepiorka; MO - A Krauss

DCP-V: Deputy DD - B Booth; DD - A Rahman

-----  
**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
-----

/s/  
-----

LIANG LI  
12/06/2018

RUBY LEONG  
12/06/2018

NAM ATIQR RAHMAN  
12/07/2018  
I concur.