CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21986Orig1s020

Trade Name:	**SPRYCEL**
Generic or Proper Name:	(dasatinib)
Sponsor:	BRISTOL MYERS SQUIBB CO
Approval Date:	November 9, 2017
Indication:	**SPRYCEL** is a kinase inhibitor indicated for the treatment of : • newly diagnosed adults with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase • adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with the resistance or intolerance to prior therapy including imatinib • adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy • pediatric patients with Ph+ CML in chronic phase .

CENTER FOR DRUG EVALUATION AND RESEARCH

21986Orig1s020

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Summary Review	
Officer/Employee List	
Division Director Memo	**X**
Cross Discipline Team Leader Review	**X**
Clinical Review(s)	**X**
Product Quality Review(s)	
Non-Clinical Review(s)	
Statistical Review(s)	
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	**X**
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21986Orig1s020

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021986/S-020

SUPPLEMENT APPROVAL

Bristol-Myers Squibb Company
Attention: Marie-Laure Papi, PharmD
Director, Global Regulatory Sciences, Oncology
PO Box 5326, Mailstop D-3291
Princeton, NJ 08543-5326

Dear Dr. Papi:

Please refer to your Supplemental New Drug Application (sNDA) dated May 9, 2017, received May 9, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Sprycel® (dasatinib) 20 mg, 50 mg, 70 mg, 80 mg, 100 mg, and 140 mg tablets.

This Prior Approval supplemental new drug application provides for a new indication for the treatment of pediatric patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert), with the addition of any labeling changes in pending "Changes Being

Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the carton and immediate-container labels submitted on September 27, 2017, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 021986/S-020**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory

comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please contact Wan Lee, Regulatory Project Manager, at (240) 402-6583.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN T FARRELL
11/09/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21986Orig1s020

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SPRYCEL® safely and effectively. See full prescribing information for SPRYCEL.

SPRYCEL (dasatinib) tablets, for oral use
Initial U.S. Approval: 2006

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	11/2017
Dosage and Administration (2)	11/2017
Warnings and Precautions (5)	11/2017

----------INDICATIONS AND USAGE----------

SPRYCEL is a kinase inhibitor indicated for the treatment of

- newly diagnosed adults with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. (1, 14)
- adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib. (1, 14)
- adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy. (1, 14)
- pediatric patients with Ph+ CML in chronic phase (1, 14)

----------DOSAGE AND ADMINISTRATION----------

- Chronic phase CML in adults: 100 mg once daily. (2)
- Accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL in adults: 140 mg once daily. (2)
- Chronic phase CML in pediatrics: starting dose based on body weight. (2)
- Administer orally, with or without a meal. Do not crush, cut, or chew tablets. (2)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 20 mg, 50 mg, 70 mg, 80 mg, 100 mg, and 140 mg. (3, 16)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- *Myelosuppression and Bleeding Events:* Severe thrombocytopenia, neutropenia, and anemia may occur. Use caution if used concomitantly with medications that inhibit platelet function or anticoagulants. Monitor complete blood counts regularly. Transfuse and interrupt SPRYCEL when indicated. (2.3, 5.1, 5.2, 6.1)
- *Fluid Retention:* Fluid retention, sometimes severe, including pleural effusions. Manage with supportive care measures and/or dose modification. (2.3, 5.3, 6.1)
- *Cardiac Dysfunction:* Monitor patients for signs or symptoms and treat appropriately. (5.4, 6.1)
- *Pulmonary Arterial Hypertension (PAH):* SPRYCEL may increase the risk of developing PAH which may be reversible on discontinuation. Consider baseline risk and evaluate patients for signs and symptoms of PAH during treatment. Stop SPRYCEL if PAH is confirmed. (5.5)
- *QT Prolongation:* Use SPRYCEL with caution in patients who have or may develop prolongation of the QT interval. (5.6)
- *Severe Dermatologic Reactions:* Individual cases of severe mucocutaneous dermatologic reactions have been reported. (5.7, 6.4)
- *Tumor Lysis Syndrome:* Tumor lysis syndrome has been reported. Maintain adequate hydration and correct uric acid levels prior to initiating therapy with SPRYCEL. (5.8)
- *Embryo-Fetal Toxicity:* Can cause fetal harm. Advise of potential risk to fetus and avoid pregnancy. (5.9, 8.1, 8.3)
- *Effects on Growth and Development in Pediatric Patients:* epiphyses delayed fusion, osteopenia, growth retardation, and gynecomastia have been reported. Monitor bone growth and development in pediatric patients. (5.10, 6.3)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥15%) in patients included myelosuppression, fluid retention events, diarrhea, headache, skin rash, hemorrhage, dyspnea, fatigue, nausea, and musculoskeletal pain. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- *Strong CYP3A4 Inhibitors:* Dose reduction may be necessary. (2.1, 7.1)
- *Strong CYP3A4 Inducers:* Dose increase may be necessary. (2.1, 7.2)
- *Antacids:* Avoid simultaneous administration. (7.2)
- *H_2 Antagonists and Proton Pump Inhibitors:* Avoid coadministration. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- *Lactation:* Not recommended (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SPRYCEL (dasatinib) is indicated for the treatment of adult patients with

- newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase.
- chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib.
- Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy.

SPRYCEL (dasatinib) is indicated for the treatment of pediatric patients with

- Ph+ CML in chronic phase.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage of SPRYCEL in Adult Patients

The recommended starting dosage of SPRYCEL for chronic phase CML in adults is 100 mg administered orally once daily. The recommended starting dosage of SPRYCEL for accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL in adults is 140 mg administered orally once daily. Tablets should not be crushed, cut, or chewed; they should be swallowed whole. SPRYCEL can be taken with or without a meal, either in the morning or in the evening.

2.2 Dosage of SPRYCEL in Pediatric Patients

The recommended starting dosage for pediatrics is based on body weight as shown in Table 1. 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. The exposure in patients receiving a crushed tablet is lower than in those swallowing an intact tablet.

Table 1: Dosage of SPRYCEL for Pediatric Patients

Body Weight (kg)[a]	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

[a]Tablet dosing is not recommended for patients weighing less than 10 kg.

2.3 Dose Modification

Strong CYP3A4 Inducers

Avoid the use of concomitant strong CYP3A4 inducers and St. John's wort. If patients must be coadministered a strong CYP3A4 inducer, consider a SPRYCEL dose increase. If the dose of SPRYCEL is increased, monitor the patient carefully for toxicity *[see Drug Interactions (7.2)]*.

Strong CYP3A4 Inhibitors

Avoid the use of concomitant strong CYP3A4 inhibitors and grapefruit juice. Recommend selecting an alternate concomitant medication with no or minimal enzyme inhibition potential, if possible. If SPRYCEL must be administered with a strong CYP3A4 inhibitor, consider a dose decrease to:

- 40 mg daily for patients taking SPRYCEL 140 mg daily.
- 20 mg daily for patients taking SPRYCEL 100 mg daily.
- 20 mg daily for patients taking SPRYCEL 70 mg daily.

For patients taking SPRYCEL 60 mg or 40 mg daily, stop SPRYCEL until the inhibitor is discontinued. Allow a washout period of approximately 1 week after the inhibitor is stopped before reinitiating SPRYCEL.

These reduced doses of SPRYCEL are predicted to adjust the area under the curve (AUC) to the range observed without CYP3A4 inhibitors; however, clinical data is not available with these dose adjustments in patients receiving strong CYP3A4 inhibitors. If SPRYCEL is not tolerated after dose reduction, either discontinue the strong CYP3A4 inhibitor or stop SPRYCEL until the inhibitor is discontinued. Allow a washout period of approximately 1 week after the inhibitor is stopped before the SPRYCEL dose is increased *[see Drug Interactions (7.1)]*.

2.4 Dose Escalation

In clinical studies of adult CML and Ph+ ALL patients, dose escalation to 140 mg once daily (chronic phase CML) or 180 mg once daily (advanced phase CML and Ph+ ALL) was allowed in patients who did not achieve a hematologic or cytogenetic response at the recommended starting dosage.

Escalate the SPRYCEL dose as shown in Table 3 in pediatric patients who do not achieve a hematologic or cytogenetic response at the recommended starting dosage.

Table 2: Dose Escalation for Pediatric CML

Formulation	**Dose (maximum dose per day)**	
	Starting Dose	**Escalation**
Tablets	40 mg	50 mg
	60 mg	70 mg
	70 mg	90 mg
	100 mg	120 mg

2.5 Dose Adjustment for Adverse Reactions

Myelosuppression

In clinical studies, myelosuppression was managed by dose interruption, dose reduction, or discontinuation of study therapy. Hematopoietic growth factor has been used in patients with resistant myelosuppression. Guidelines for dose modifications for adult and pediatric patients are summarized in Tables 4 and 5, respectively.

Table 3: Dose Adjustments for Neutropenia and Thrombocytopenia in Adults

Chronic Phase CML (starting dose 100 mg once daily)	ANC* $<0.5 \times 10^9$/L or Platelets $<50 \times 10^9$/L	1. Stop SPRYCEL until ANC $\geq 1.0 \times 10^9$/L and platelets $\geq 50 \times 10^9$/L. 2. Resume treatment with SPRYCEL at the original starting dose if recovery occurs in ≤7 days. 3. If platelets $<25 \times 10^9$/L or recurrence of ANC $<0.5 \times 10^9$/L for >7 days, repeat Step 1 and resume SPRYCEL at a reduced dose of 80 mg once daily for second episode. For third episode, further reduce dose to 50 mg once daily (for newly diagnosed patients) or discontinue SPRYCEL (for patients resistant or intolerant to prior therapy including imatinib).
Accelerated Phase CML, Blast Phase CML and Ph+ ALL (starting dose 140 mg once daily)	ANC* $<0.5 \times 10^9$/L or Platelets $<10 \times 10^9$/L	1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukemia, stop SPRYCEL until ANC $\geq 1.0 \times 10^9$/L and platelets $\geq 20 \times 10^9$/L and resume at the original starting dose. 3. If recurrence of cytopenia, repeat Step 1 and resume SPRYCEL at a reduced dose of 100 mg once daily (second episode) or 80 mg once daily (third episode). 4. If cytopenia is related to leukemia, consider dose escalation to 180 mg once daily.

*ANC: absolute neutrophil count

Table 4: Dose Adjustments for Neutropenia and Thrombocytopenia in Pediatric Patients

		Dose (maximum dose per day)		
1. If cytopenia persists for more than 3 weeks, check if cytopenia is related to leukemia (marrow aspirate or biopsy).		**Original Starting Dose**	**One-Level Dose Reduction**	**Two-Level Dose Reduction**
	Tablets	40 mg	20 mg	**
		60 mg	40 mg	20 mg

Table 4: Dose Adjustments for Neutropenia and Thrombocytopenia in Pediatric Patients

	Dose (maximum dose per day)		
2. If cytopenia is unrelated to leukemia, stop SPRYCEL until ANC* $\geq 1.0 \times 10^9$/L and platelets $\geq 75 \times 10^9$/L and resume at the original starting dose or at a reduced dose.	70 mg	60 mg	50 mg
	100 mg	80 mg	70 mg
3. If cytopenia recurs, repeat marrow aspirate/biopsy and resume SPRYCEL at a reduced dose.			

*ANC: absolute neutrophil count
** lower tablet dose not available

For all pediatric patients, if Grade ≥ 3 neutropenia or thrombocytopenia recurs during complete hematologic response (CHR), interrupt SPRYCEL and resume at a reduced dose. Implement temporary dose reductions for intermediate degrees of cytopenia and disease response as needed.

Non-Hematologic Adverse Reactions

If a severe non-hematologic adverse reaction develops with SPRYCEL use, treatment must be withheld until the event has resolved or improved. Thereafter, treatment can be resumed as appropriate at a reduced dose depending on the severity and recurrence of the event *[see Warnings and Precautions (5.1)]*.

2.6 Duration of Treatment

In clinical studies, treatment with SPRYCEL in adults and pediatric patients 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 response (including complete cytogenetic response [CCyR]) or major molecular response (MMR and MR4.5) has not been established.

SPRYCEL is an antineoplastic product. Follow applicable special handling and disposal procedures.[1]

3 DOSAGE FORMS AND STRENGTHS

SPRYCEL (dasatinib) Tablets are available as 20-mg, 50-mg, 70-mg, 80-mg, 100-mg, and 140-mg white to off-white, biconvex, film-coated tablets *[see How Supplied (16.1)]*.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Treatment with SPRYCEL is associated with severe (NCI CTCAE Grade 3 or 4) thrombocytopenia, neutropenia, and anemia, which occur earlier and more frequently in patients with advanced phase CML or Ph+ ALL than in patients with chronic phase CML.

In patients with chronic phase CML, perform complete blood counts (CBCs) every 2 weeks for 12 weeks, then every 3 months thereafter, or as clinically indicated. In patients with advanced phase CML or Ph+ ALL, perform CBCs weekly for the first 2 months and then monthly thereafter, or as clinically indicated.

Myelosuppression is generally reversible and usually managed by withholding SPRYCEL temporarily and/or dose reduction *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)]*.

5.2 Bleeding-Related Events

SPRYCEL can cause serious and fatal bleeding. In all CML or Ph+ ALL clinical studies, Grade ≥3 central nervous system (CNS) hemorrhages, including fatalities, occurred in <1% of patients receiving SPRYCEL. The incidence of Grade 3/4 hemorrhage, occurred in 5.8% of adult patients and generally required treatment interruptions and transfusions. The incidence of Grade 5 hemorrhage occurred in 0.4% of adult patients. The most frequent site of hemorrhage was gastrointestinal. Most bleeding events in clinical studies were associated with severe thrombocytopenia. In addition to causing thrombocytopenia in human subjects, dasatinib caused platelet dysfunction *in vitro*.

Concomitant medications that inhibit platelet function or anticoagulants may increase the risk of hemorrhage.

5.3 Fluid Retention

SPRYCEL may cause fluid retention. After 5 years of follow-up in the adult randomized newly diagnosed chronic phase CML study (n=258), Grade 3 or 4 fluid retention was reported in 5% of patients, including 3% of patients with Grade 3 or 4 pleural effusion. In adult patients with newly diagnosed or imatinib-resistant or -intolerant chronic phase CML, Grade 3 or 4 fluid retention occurred in 6% of patients treated with SPRYCEL at the recommended dose (n=548). In adult patients with advanced phase CML or Ph+ ALL treated with SPRYCEL at the recommended dose (n=304), Grade 3 or 4 fluid retention was reported in 8% of patients, including Grade 3 or 4 pleural effusion reported in 7% of patients. In pediatric patients with chronic phase CML, cases of Grade 1 or 2 fluid retention were reported in 10.3% of patients.

Evaluate patients who develop symptoms of pleural effusion or other fluid retention, such as new or worsened dyspnea on exertion or at rest, pleuritic chest pain, or dry cough, promptly with a chest x-ray or additional diagnostic imaging as appropriate. Fluid retention events were typically

managed by supportive care measures that may include diuretics or short courses of steroids. Severe pleural effusion may require thoracentesis and oxygen therapy. Consider dose reduction or treatment interruption *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)]*.

5.4 Cardiovascular Events

SPRYCEL can cause cardiac dysfunction. After 5 years of follow-up in the randomized newly diagnosed chronic phase CML trial in adults (n=258), the following cardiac adverse reactions occurred: cardiac ischemic events (3.9% dasatinib vs 1.6% imatinib), cardiac-related fluid retention (8.5% dasatinib vs 3.9% imatinib), and conduction system abnormalities, most commonly arrhythmia and palpitations (7.0% dasatinib vs 5.0% imatinib). Two cases (0.8%) of peripheral arterial occlusive disease occurred with imatinib and 2 (0.8%) transient ischemic attacks occurred with dasatinib. Monitor patients for signs or symptoms consistent with cardiac dysfunction and treat appropriately.

5.5 Pulmonary Arterial Hypertension

SPRYCEL may increase the risk of developing pulmonary arterial hypertension (PAH) in adult and pediatric patients which may occur any time after initiation, including after more than 1 year of treatment. Manifestations include dyspnea, fatigue, hypoxia, and fluid retention. PAH may be reversible on discontinuation of SPRYCEL. Evaluate patients for signs and symptoms of underlying cardiopulmonary disease prior to initiating SPRYCEL and during treatment. If PAH is confirmed, SPRYCEL should be permanently discontinued.

5.6 QT Prolongation

SPRYCEL may increase the risk of prolongation of QTc in patients including those with hypokalemia or hypomagnesemia, patients with congenital long QT syndrome, patients taking antiarrhythmic medicines or other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy. Correct hypokalemia or hypomagnesemia prior to and during SPRYCEL administration.

5.7 Severe Dermatologic Reactions

Cases of severe mucocutaneous dermatologic reactions, including Stevens-Johnson syndrome and erythema multiforme, have been reported in patients treated with SPRYCEL. Discontinue permanently in patients who experience a severe mucocutaneous reaction during treatment if no other etiology can be identified.

5.8 Tumor Lysis Syndrome

Tumor lysis syndrome has been reported in patients with resistance to prior imatinib therapy, primarily in advanced phase disease. Due to potential for tumor lysis syndrome, maintain adequate hydration, correct uric acid levels prior to initiating therapy with SPRYCEL, and monitor electrolyte levels. Patients with advanced stage disease and/or high tumor burden may be at increased risk and should be monitored more frequently *[see Adverse Reactions (6.3)]*.

5.9 Embryo-Fetal Toxicity

Based on limited human data, SPRYCEL can cause fetal harm when administered to a pregnant woman. Adverse pharmacologic effects of SPRYCEL including hydrops fetalis, fetal leukopenia, and fetal thrombocytopenia have been reported with maternal exposure to SPRYCEL. Advise females of reproductive potential to avoid pregnancy, which may include the use of effective contraception, during treatment with SPRYCEL and for 30 days after the final dose *[see Use in Specific Populations (8.1, 8.3)]*.

5.10 Effects on Growth and Development in Pediatric Patients

In pediatric trials of SPRYCEL in chronic phase CML after at least 2 years of treatment, adverse reactions associated with bone growth and development were reported in 5 (5.2%) patients, one of which was severe in intensity (Growth Retardation Grade 3). These 5 cases included cases of epiphyses delayed fusion, osteopenia, growth retardation, and gynecomastia *[see Adverse Reactions (6.2) and Use in Specific Populations (8.4)]*. Of these 5 cases, 1 case of osteopenia and 1 case of gynecomastia resolved during treatment.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Myelosuppression *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)]*.
- Bleeding-related events *[see Warnings and Precautions (5.2)]*.
- Fluid retention *[see Warnings and Precautions (5.3)]*.
- Cardiovascular events *[see Warnings and Precautions (5.4)]*.
- Pulmonary arterial hypertension *[see Warnings and Precautions (5.5)]*.
- QT prolongation *[see Warnings and Precautions (5.6)]*.
- Severe dermatologic reactions *[see Warnings and Precautions (5.7)]*.
- Tumor lysis syndrome *[see Warnings and Precautions (5.8)]*.
- Effects on growth and development in pediatric patients *[see Warnings and Precautions (5.10)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to SPRYCEL at all doses tested in clinical studies (n=2809), including 324 adult patients with newly diagnosed chronic phase CML, 2388 adult patients with imatinib-resistant or -intolerant chronic or advanced phase CML or Ph+ ALL, and 97 pediatric patients with chronic phase CML. The median duration of therapy in a total of 2712 adult patients was 19.2 months (range 0 to 93.2 months). In a randomized trial in patients with newly diagnosed chronic phase CML, the median duration of therapy was approximately 60

months. The median duration of therapy in 1618 adult patients with chronic phase CML was 29 months (range 0 to 92.9 months).

The median duration of therapy in 1094 adult patients with advanced phase CML or Ph+ ALL was 6.2 months (range 0 to 93.2 months).

In two non-randomized trials in 97 pediatric patients with chronic phase CML (51 patients newly diagnosed and 46 patients resistant or intolerant to previous treatment with imatinib), the median duration of therapy was 51.1 months (range 1.9 to 99.6 months).

In the overall population of 2712 adult patients, 88% of patients experienced adverse reactions at some time and 19% experienced adverse reactions leading to treatment discontinuation.

In the randomized trial in adult patients with newly diagnosed chronic phase CML, drug was discontinued for adverse reactions in 16% of patients with a minimum of 60 months of follow-up. After a minimum of 60 months of follow-up, the cumulative discontinuation rate was 39%. Among the 1618 patients with chronic phase CML, drug-related adverse reactions leading to discontinuation were reported in 329 (20.3%) patients; among the 1094 patients with advanced phase CML or Ph+ ALL, drug-related adverse reactions leading to discontinuation were reported in 191 (17.5%) patients.

Among the 97 pediatric subjects, drug-related adverse reactions leading to discontinuation were reported in 1 patient (1%).

Adverse reactions reported in ≥10% of adult patients, and other adverse reactions of interest, in a randomized trial in patients with newly diagnosed chronic phase CML at a median follow-up of approximately 60 months are presented in Table 6.

Adverse reactions reported in ≥10% of adult patients treated at the recommended dose of 100 mg once daily (n=165), and other adverse reactions of interest, in a randomized dose-optimization trial of patients with chronic phase CML resistant or intolerant to prior imatinib therapy at a median follow-up of approximately 84 months are presented in Table 8.

Adverse reactions reported in ≥10% of pediatric patients at a median follow-up of approximately 51.1 months are presented in Table 11.

Drug-related serious adverse reactions (SARs) were reported for 16.7% of adult patients in the randomized trial of patients with newly diagnosed chronic phase CML. Serious adverse reactions reported in ≥5% of patients included pleural effusion (5%).

Drug-related SARs were reported for 26.1% of patients treated at the recommended dose of 100 mg once daily in the randomized dose-optimization trial of adult patients with chronic phase CML resistant or intolerant to prior imatinib therapy. Serious adverse reactions reported in ≥5% of patients included pleural effusion (10%).

Drug-related SARs were reported for 14.4% of pediatric patients.

Chronic Myeloid Leukemia (CML)

Adverse reactions (excluding laboratory abnormalities) that were reported in at least 10% of adult patients are shown in Table 6 for newly diagnosed patients with chronic phase CML and Tables 8 and 10 for CML patients with resistance or intolerance to prior imatinib therapy.

Table 5: Adverse Reactions Reported in ≥10% of Adult Patients with Newly Diagnosed Chronic Phase CML (minimum of 60 months follow-up)

	All Grades		Grade 3/4	
	SPRYCEL (n=258)	Imatinib (n=258)	SPRYCEL (n=258)	Imatinib (n=258)
Adverse Reaction	**Percent (%) of Patients**			
Fluid retention	38	45	5	1
Pleural effusion	28	1	3	0
Superficial localized edema	14	38	0	<1
Pulmonary hypertension	5	<1	1	0
Generalized edema	4	7	0	0
Pericardial effusion	4	1	1	0
Congestive heart failure/ cardiac dysfunction[a]	2	1	<1	<1
Pulmonary edema	1	0	0	0
Diarrhea	22	23	1	1
Musculoskeletal pain	14	17	0	<1
Rash[b]	14	18	0	2
Headache	14	11	0	0
Abdominal pain	11	8	0	1
Fatigue	11	12	<1	0
Nausea	10	25	0	0
Myalgia	7	12	0	0
Arthralgia	7	10	0	<1
Hemorrhage[c]	8	8	1	1
Gastrointestinal bleeding	2	2	1	0
Other bleeding[d]	6	6	0	<1
CNS bleeding	<1	<1	0	<1
Vomiting	5	12	0	0
Muscle spasms	5	21	0	<1

[a] Includes cardiac failure acute, cardiac failure congestive, cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and left ventricular dysfunction.

[b] Includes erythema, erythema multiforme, rash, rash generalized, rash macular, rash papular, rash pustular, skin exfoliation, and rash vesicular.

[c] Adverse reaction of special interest with <10% frequency.

[d] Includes conjunctival hemorrhage, ear hemorrhage, ecchymosis, epistaxis, eye hemorrhage, gingival bleeding, hematoma, hematuria, hemoptysis, intra-abdominal hematoma, petechiae, scleral hemorrhage, uterine hemorrhage, and vaginal hemorrhage.

A comparison of cumulative rates of adverse reactions reported in ≥10% of patients with minimum follow-up of 1 and 5 years in a randomized trial of newly diagnosed patients with chronic phase CML treated with SPRYCEL are shown in Table 7.

Table 6: Adverse Reactions Reported in ≥10% of Adult Patients with Newly Diagnosed Chronic Phase CML in the SPRYCEL-Treated Arm (n=258)

	Minimum of 1 Year Follow-up		Minimum of 5 Years Follow-up	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Adverse Reaction	Percent (%) of Patients			
Fluid retention	19	1	38	5
Pleural effusion	10	0	28	3
Superficial localized edema	9	0	14	0
Pulmonary hypertension	1	0	5	1
Generalized edema	2	0	4	0
Pericardial effusion	1	<1	4	1
Congestive heart failure/cardiac dysfunction[a]	2	<1	2	<1
Pulmonary edema	<1	0	1	0
Diarrhea	17	<1	22	1
Musculoskeletal pain	11	0	14	0
Rash[b]	11	0	14	0
Headache	12	0	14	0
Abdominal pain	7	0	11	0
Fatigue	8	<1	11	<1
Nausea	8	0	10	0

[a] Includes cardiac failure acute, cardiac failure congestive, cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and left ventricular dysfunction.

[b] Includes erythema, erythema multiforme, rash, rash generalized, rash macular, rash papular, rash pustular, skin exfoliation, and rash vesicular.

At 60 months, there were 26 deaths in dasatinib-treated patients (10.1%) and 26 deaths in imatinib-treated patients (10.1%); 1 death in each group was assessed by the investigator as related to study therapy.

Table 7: Adverse Reactions Reported in ≥10% of Adult Patients with Chronic Phase CML Resistant or Intolerant to Prior Imatinib Therapy (minimum of 84 months follow-up)

	100 mg Once Daily	
	Chronic (n=165)	
	All Grades	Grade 3/4
Adverse Reaction	**Percent (%) of Patients**	
Fluid retention	48	7
Superficial localized edema	22	0
Pleural effusion	28	5
Generalized edema	4	0
Pericardial effusion	3	1
Pulmonary hypertension	2	1
Headache	33	1
Diarrhea	28	2
Fatigue	26	4
Dyspnea	24	2
Musculoskeletal pain	22	2
Nausea	18	1
Skin rash[a]	18	2
Myalgia	13	0
Arthralgia	13	1
Infection (including bacterial, viral, fungal, and non-specified)	13	1
Abdominal pain	12	1
Hemorrhage	12	1
Gastrointestinal bleeding	2	1
Pruritus	12	1
Pain	11	1
Constipation	10	1

[a] Includes drug eruption, erythema, erythema multiforme, erythrosis, exfoliative rash, generalized erythema, genital rash, heat rash, milia, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, skin exfoliation, skin irritation, urticaria vesiculosa, and rash vesicular.

Cumulative rates of selected adverse reactions that were reported over time in patients treated with the 100 mg once daily recommended starting dose in a randomized dose-optimization trial of imatinib-resistant or -intolerant patients with chronic phase CML are shown in Table 9.

Table 8: Selected Adverse Reactions Reported in Adult Dose Optimization Trial (Imatinib-Intolerant or -Resistant Chronic Phase CML)[a]

	Minimum of 2 Years Follow-up		Minimum of 5 Years Follow-up		Minimum of 7 Years Follow-up	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Adverse Reaction	**Percent (%) of Patients**					
Diarrhea	27	2	28	2	28	2
Fluid retention	34	4	42	6	48	7
Superficial edema	18	0	21	0	22	0
Pleural effusion	18	2	24	4	28	5
Generalized edema	3	0	4	0	4	0
Pericardial effusion	2	1	2	1	3	1
Pulmonary hypertension	0	0	0	0	2	1
Hemorrhage	11	1	11	1	12	1
Gastrointestinal bleeding	2	1	2	1	2	1

[a] Randomized dose-optimization trial results reported in the recommended starting dose of 100 mg once daily (n=165) population.

Table 9: Adverse Reactions Reported in ≥10% of Adult Patients with Advanced Phase CML Resistant or Intolerant to Prior Imatinib Therapy

	140 mg Once Daily					
	Accelerated (n=157)		Myeloid Blast (n=74)		Lymphoid Blast (n=33)	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Adverse Reaction	**Percent (%) of Patients**					
Fluid retention	35	8	34	7	21	6
Superficial localized edema	18	1	14	0	3	0
Pleural effusion	21	7	20	7	21	6
Generalized edema	1	0	3	0	0	0
Pericardial effusion	3	1	0	0	0	0
Congestive heart failure/cardiac dysfunction[a]	0	0	4	0	0	0
Pulmonary edema	1	0	4	3	0	0
Headache	27	1	18	1	15	3
Diarrhea	31	3	20	5	18	0
Fatigue	19	2	20	1	9	3
Dyspnea	20	3	15	3	3	3

Table 9: Adverse Reactions Reported in ≥10% of Adult Patients with Advanced Phase CML Resistant or Intolerant to Prior Imatinib Therapy

	140 mg Once Daily					
	Accelerated (n=157)		Myeloid Blast (n=74)		Lymphoid Blast (n=33)	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Adverse Reaction	Percent (%) of Patients					
Musculoskeletal pain	11	0	8	1	0	0
Nausea	19	1	23	1	21	3
Skin rash[b]	15	0	16	1	21	0
Arthralgia	10	0	5	1	0	0
Infection (including bacterial, viral, fungal, and non-specified)	10	6	14	7	9	0
Hemorrhage	26	8	19	9	24	9
Gastrointestinal bleeding	8	6	9	7	9	3
CNS bleeding	1	1	0	0	3	3
Vomiting	11	1	12	0	15	0
Pyrexia	11	2	18	3	6	0
Febrile neutropenia	4	4	12	12	12	12

[a] Includes ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and ventricular failure.

[b] Includes drug eruption, erythema, erythema multiforme, erythrosis, exfoliative rash, generalized erythema, genital rash, heat rash, milia, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, skin exfoliation, skin irritation, urticaria vesiculosa, and rash vesicular.

Table 10: Adverse Reactions Reported in ≥10% of Dasatinib-Treated Pediatric Patients (n=97)

	All Grades	Grade 3/4
Adverse Reaction	**Percent (%) of Patients**	
Headache	28	3
Nausea	20	0
Diarrhea	21	0
Skin rash	19	0
Vomiting	13	0
Pain in extremity	19	1
Abdominal pain	16	0
Fatigue	10	0
Arthralgia	10	1

Laboratory Abnormalities

Myelosuppression was commonly reported in all patient populations. The frequency of Grade 3 or 4 neutropenia, thrombocytopenia, and anemia was higher in patients with advanced phase CML than in chronic phase CML (Tables 12 and 13). Myelosuppression was reported in patients with normal baseline laboratory values as well as in patients with pre-existing laboratory abnormalities.

In patients who experienced severe myelosuppression, recovery generally occurred following dose interruption or reduction; permanent discontinuation of treatment occurred in 2% of adult patients with newly diagnosed chronic phase CML and 5% of adult patients with resistance or intolerance to prior imatinib therapy *[see Warnings and Precautions (5.1)]*.

Grade 3 or 4 elevations of transaminases or bilirubin and Grade 3 or 4 hypocalcemia, hypokalemia, and hypophosphatemia were reported in patients with all phases of CML but were reported with an increased frequency in patients with myeloid or lymphoid blast phase CML. Elevations in transaminases or bilirubin were usually managed with dose reduction or interruption. Patients developing Grade 3 or 4 hypocalcemia during SPRYCEL therapy often had recovery with oral calcium supplementation.

Laboratory abnormalities reported in adult patients with newly diagnosed chronic phase CML are shown in Table 12. There were no discontinuations of SPRYCEL therapy in this patient population due to biochemical laboratory parameters.

Table 11: CTC Grade 3/4 Laboratory Abnormalities in Adult Patients with Newly Diagnosed Chronic Phase CML (minimum of 60 months follow-up)

	SPRYCEL (n=258)	Imatinib (n=258)
	Percent (%) of Patients	
Hematology Parameters		
Neutropenia	29	24
Thrombocytopenia	22	14
Anemia	13	9
Biochemistry Parameters		
Hypophosphatemia	7	31
Hypokalemia	0	3
Hypocalcemia	4	3
Elevated SGPT (ALT)	<1	2
Elevated SGOT (AST)	<1	1
Elevated Bilirubin	1	0
Elevated Creatinine	1	1

CTC grades: neutropenia (Grade 3 ≥0.5–<1.0 × 10^9/L, Grade 4 <0.5 × 10^9/L); thrombocytopenia (Grade 3 ≥25–<50 × 10^9/L, Grade 4 <25 × 10^9/L); anemia (hemoglobin Grade 3 ≥65–<80 g/L, Grade 4 <65 g/L); elevated creatinine (Grade 3 >3–6 × upper limit of normal range (ULN), Grade 4 >6 × ULN); elevated bilirubin (Grade 3 >3–10 × ULN, Grade 4 >10 × ULN); elevated SGOT or SGPT (Grade 3 >5–20 × ULN, Grade 4 >20 × ULN); hypocalcemia (Grade 3 <7.0–6.0 mg/dL, Grade 4 <6.0 mg/dL); hypophosphatemia (Grade 3 <2.0–1.0 mg/dL, Grade 4 <1.0 mg/dL); hypokalemia (Grade 3 <3.0–2.5 mmol/L, Grade 4 <2.5 mmol/L).

Laboratory abnormalities reported in patients with CML resistant or intolerant to imatinib who received the recommended starting doses of SPRYCEL are shown by disease phase in Table 13.

Table 12: CTC Grade 3/4 Laboratory Abnormalities in Clinical Studies of CML in Adults: Resistance or Intolerance to Prior Imatinib Therapy

	Chronic Phase CML 100 mg Once Daily	Advanced Phase CML 140 mg Once Daily		
	(n=165)	Accelerated Phase (n=157)	Myeloid Blast Phase (n=74)	Lymphoid Blast Phase (n=33)
	Percent (%) of Patients			
Hematology Parameters*				
Neutropenia	36	58	77	79
Thrombocytopenia	24	63	78	85
Anemia	13	47	74	52
Biochemistry Parameters				
Hypophosphatemia	10	13	12	18
Hypokalemia	2	7	11	15
Hypocalcemia	<1	4	9	12
Elevated SGPT (ALT)	0	2	5	3
Elevated SGOT (AST)	<1	0	4	3
Elevated Bilirubin	<1	1	3	6
Elevated Creatinine	0	2	8	0

CTC grades: neutropenia (Grade 3 ≥0.5–<1.0 × 10^9/L, Grade 4 <0.5 × 10^9/L); thrombocytopenia (Grade 3 ≥25–<50 × 10^9/L, Grade 4 <25 × 10^9/L); anemia (hemoglobin Grade 3 ≥65–<80 g/L, Grade 4 <65 g/L); elevated creatinine (Grade 3 >3–6 × upper limit of normal range (ULN), Grade 4 >6 × ULN); elevated bilirubin (Grade 3 >3–10 × ULN, Grade 4 >10 × ULN); elevated SGOT or SGPT (Grade 3 >5–20 × ULN, Grade 4 >20 × ULN); hypocalcemia (Grade 3 <7.0–6.0 mg/dL, Grade 4 <6.0 mg/dL); hypophosphatemia (Grade 3 <2.0–1.0 mg/dL, Grade 4 <1.0 mg/dL); hypokalemia (Grade 3 <3.0–2.5 mmol/L, Grade 4 <2.5 mmol/L).

* Hematology parameters for 100 mg once-daily dosing in chronic phase CML reflects 60-month minimum follow-up.

Among adult patients with chronic phase CML with resistance or intolerance to prior imatinib therapy, cumulative Grade 3 or 4 cytopenias were similar at 2 and 5 years including: neutropenia (36% vs 36%), thrombocytopenia (23% vs 24%), and anemia (13% vs 13%).

In the pediatric studies, the rates of laboratory abnormalities were consistent with the known profile for laboratory parameters in adults.

Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL) in Adults

A total of 135 patients with Ph+ ALL were treated with SPRYCEL in clinical studies. The median duration of treatment was 3 months (range 0.03–31 months). The safety profile of patients with Ph+ ALL was similar to those with lymphoid blast phase CML. The most frequently reported adverse reactions included fluid retention events, such as pleural effusion (24%) and superficial edema (19%), and gastrointestinal disorders, such as diarrhea (31%), nausea (24%), and vomiting (16%). Hemorrhage (19%), pyrexia (17%), rash (16%), and dyspnea (16%) were also frequently

reported. Serious adverse reactions reported in ≥5% of patients included pleural effusion (11%), gastrointestinal bleeding (7%), febrile neutropenia (6%), and infection (5%).

6.2 Additional Pooled Data from Clinical Trials

The following additional adverse reactions were reported in adult and pediatric patients (n=2809) in SPRYCEL CML and Ph+ ALL clinical studies at a frequency of ≥10%, 1%–<10%, 0.1%–<1%, or <0.1%. These adverse reactions are included based on clinical relevance.

Gastrointestinal Disorders: *1%–<10%* – mucosal inflammation (including mucositis/stomatitis), dyspepsia, abdominal distension, constipation, gastritis, colitis (including neutropenic colitis), oral soft tissue disorder; *0.1%–<1%* – ascites, dysphagia, anal fissure, upper gastrointestinal ulcer, esophagitis, pancreatitis, gastroesophageal reflux disease; *<0.1%* – protein losing gastroenteropathy, ileus, acute pancreatitis, anal fistula.

General Disorders and Administration-Site Conditions: *≥10%* – peripheral edema, face edema; *1%–<10%* – asthenia, chest pain, chills; *0.1%–<1%* – malaise, other superficial edema, peripheral swelling; *<0.1%* – gait disturbance.

Skin and Subcutaneous Tissue Disorders: *1%–<10%* – alopecia, acne, dry skin, hyperhidrosis, urticaria, dermatitis (including eczema); *0.1%–<1%* – pigmentation disorder, skin ulcer, bullous conditions, photosensitivity, nail disorder, neutrophilic dermatosis, panniculitis, palmar-plantar erythrodysesthesia syndrome, hair disorder; *<0.1%* – leukocytoclastic vasculitis, skin fibrosis.

Respiratory, Thoracic, and Mediastinal Disorders: *1%–<10%* – lung infiltration, pneumonitis, cough; *0.1%–<1%* – asthma, bronchospasm, dysphonia, pulmonary arterial hypertension; *<0.1%* – acute respiratory distress syndrome, pulmonary embolism.

Nervous System Disorders: *1%–<10%* – neuropathy (including peripheral neuropathy), dizziness, dysgeusia, somnolence; *0.1%–<1%* – amnesia, tremor, syncope, balance disorder; *<0.1%* – convulsion, cerebrovascular accident, transient ischemic attack, optic neuritis, VIIth nerve paralysis, dementia, ataxia.

Blood and Lymphatic System Disorders: *0.1%–<1%* – lymphadenopathy, lymphopenia; *<0.1%* – aplasia pure red cell.

Musculoskeletal and Connective Tissue Disorders: *1%–<10%* – muscular weakness, musculoskeletal stiffness; *0.1%–<1%* – rhabdomyolysis, tendonitis, muscle inflammation, osteonecrosis, arthritis; *<0.1%* – epiphyses delayed fusion (reported at *1%–<10%* in the pediatric studies), growth retardation (reported at *1%–<10%* in the pediatric studies).

Investigations: *1%–<10%* – weight increased, weight decreased; *0.1%–<1%* – blood creatine phosphokinase increased, gamma-glutamyltransferase increased.

Infections and Infestations: *1%–<10%* – pneumonia (including bacterial, viral, and fungal), upper respiratory tract infection/inflammation, herpes virus infection, enterocolitis infection, sepsis (including fatal outcomes [0.2%]).

Metabolism and Nutrition Disorders: *1%–<10%* – appetite disturbances, hyperuricemia; *0.1%–<1%* – hypoalbuminemia, tumor lysis syndrome, dehydration, hypercholesterolemia; *<0.1%* – diabetes mellitus.

Cardiac Disorders: *1%–<10%* – arrhythmia (including tachycardia), palpitations; *0.1%–<1%* – angina pectoris, cardiomegaly, pericarditis, ventricular arrhythmia (including ventricular tachycardia), electrocardiogram T-wave abnormal, troponin increased; *<0.1%* – cor pulmonale, myocarditis, acute coronary syndrome, cardiac arrest, electrocardiogram PR prolongation, coronary artery disease, pleuropericarditis.

Eye Disorders: *1%–<10%* – visual disorder (including visual disturbance, vision blurred, and visual acuity reduced), dry eye; *0.1%–<1%* – conjunctivitis, visual impairment, lacrimation increased, *<0.1%* – photophobia.

Vascular Disorders: *1%–<10%* – flushing, hypertension; *0.1%–<1%* – hypotension, thrombophlebitis, thrombosis; *<0.1%* – livedo reticularis, deep vein thrombosis, embolism.

Psychiatric Disorders: *1%–<10%* – insomnia, depression; *0.1%–<1%* – anxiety, affect lability, confusional state, libido decreased.

Pregnancy, Puerperium, and Perinatal Conditions: *<0.1%* – abortion.

Reproductive System and Breast Disorders: *0.1%–<1%* – gynecomastia, menstrual disorder.

Injury, Poisoning, and Procedural Complications: *1%–<10%* – contusion.

Ear and Labyrinth Disorders: *1%–<10%* – tinnitus; *0.1%–<1%* – vertigo, hearing loss.

Hepatobiliary Disorders: *0.1%–<1%* – cholestasis, cholecystitis, hepatitis.

Renal and Urinary Disorders: *0.1%–<1%* – urinary frequency, renal failure, proteinuria; *<0.1%* – renal impairment.

Immune System Disorders: *0.1%–<1%* – hypersensitivity (including erythema nodosum).

Endocrine Disorders: *0.1%–<1%* – hypothyroidism; *<0.1%* – hyperthyroidism, thyroiditis.

6.3 Postmarketing Experience

The following additional adverse reactions have been identified during post approval use of SPRYCEL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections: hepatitis B virus reactivation

Cardiac disorders: atrial fibrillation/atrial flutter

Respiratory, thoracic, and mediastinal disorders: interstitial lung disease

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome

Renal and urinary disorders: nephrotic syndrome

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on Dasatinib

Strong CYP3A4 Inhibitors

The coadministration with strong CYP3A inhibitors may increase dasatinib concentrations *[see Clinical Pharmacology (12.3)]*. Increased dasatinib concentrations may increase the risk of toxicity. Avoid concomitant use of strong CYP3A4 inhibitors. If concomitant administration of a strong CYP3A4 inhibitor cannot be avoided, consider a SPRYCEL dose reduction *[see Dosage and Administration (2.3)]*.

Strong CYP3A4 Inducers

The coadministration of SPRYCEL with strong CYP3A inducers may decrease dasatinib concentrations *[see Clinical Pharmacology (12.3)]*. Decreased dasatinib concentrations may reduce efficacy. Consider alternative drugs with less enzyme induction potential. If concomitant administration of a strong CYP3A4 inducer cannot be avoided, consider a SPRYCEL dose increase.

Gastric Acid Reducing Agents

The coadministration of SPRYCEL with a gastric acid reducing agent may decrease the concentrations of dasatinib. Decreased dasatinib concentrations may reduce efficacy.

Do not administer H_2 antagonists or proton pump inhibitors with SPRYCEL. Consider the use of antacids in place of H_2 antagonists or proton pump inhibitors. Administer the antacid at least 2 hours prior to or 2 hours after the dose of SPRYCEL. Avoid simultaneous administration of SPRYCEL with antacids.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on limited human data, SPRYCEL can cause fetal harm when administered to a pregnant woman. Adverse pharmacologic effects including hydrops fetalis, fetal leukopenia, and fetal thrombocytopenia have been reported with maternal exposure to SPRYCEL. Animal reproduction studies in rats have demonstrated extensive mortality during organogenesis, the fetal period, and in neonates. Skeletal malformations were observed in a limited number of surviving rat and rabbit conceptuses. These findings occurred at dasatinib plasma concentrations below those in humans receiving therapeutic doses of dasatinib *[see Data]*. Advise a pregnant woman of the potential risk to a fetus.

The estimated background risk in the U.S. general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Transplacental transfer of dasatinib has been reported. Dasatinib has been measured in fetal plasma and amniotic fluid at concentrations comparable to those in maternal plasma. Hydrops fetalis, fetal leukopenia, and fetal thrombocytopenia have been reported with maternal exposure to dasatinib. These adverse pharmacologic effects on the fetus are similar to adverse reactions observed in adult patients and may result in fetal harm or neonatal death *[see Warnings and Precautions (5.1, 5.3)]*.

Data

Human Data

Based on human experience, dasatinib is suspected to cause congenital malformations, including neural tube defects, and harmful pharmacological effects on the fetus when administered during pregnancy.

Animal Data

In nonclinical studies at plasma concentrations below those observed in humans receiving therapeutic doses of dasatinib, embryo-fetal toxicities were observed in rats and rabbits. Fetal death was observed in rats. In both rats and rabbits, the lowest doses of dasatinib tested (rat: 2.5 mg/kg/day [15 mg/m^2/day] and rabbit: 0.5 mg/kg/day [6 mg/m^2/day]) resulted in embryo-fetal toxicities. These doses produced maternal AUCs of 105 ng•h/mL and 44 ng•h/mL (0.1-fold the human AUC) in rats and rabbits, respectively. Embryo-fetal toxicities included skeletal malformations at multiple sites (scapula, humerus, femur, radius, ribs, and clavicle), reduced ossification (sternum; thoracic, lumbar, and sacral vertebrae; forepaw phalanges; pelvis; and hyoid body), edema, and microhepatia. In a pre- and postnatal development study in rats, administration of dasatinib from gestation day (GD) 16 through lactation day (LD) 20, GD 21 through LD 20, or LD 4 through LD 20 resulted in extensive pup mortality at maternal exposures that were below the exposures in patients treated with dasatinib at the recommended labeling dose.

8.2 Lactation

Risk Summary

No data are available regarding the presence of dasatinib in human milk, the effects of the drug on the breastfed child, or the effects of the drug on milk production. However, dasatinib is present in the milk of lactating rats. Because of the potential for serious adverse reactions in nursing children from SPRYCEL, breastfeeding is not recommended during treatment with SPRYCEL and for 2 weeks after the final dose.

8.3 Females and Males of Reproductive Potential

Contraception

Females

SPRYCEL can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to avoid pregnancy, which may include the use of effective contraceptive methods, during treatment with SPRYCEL and for 30 days after the final dose.

Infertility

Based on animal data, dasatinib may result in damage to female and male reproductive tissues *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and efficacy of SPRYCEL in 97 pediatric patients with chronic phase CML were evaluated in two pediatric studies (a Phase I, open-label, non-randomized dose-ranging trial and a Phase II, open-label, non-randomized trial). Fifty-one patients (exclusively from the Phase II trial) were newly diagnosed with chronic phase CML and 46 patients (17 from the Phase I trial and 29 from the Phase II trial) were resistant or intolerant to previous treatment with imatinib. The majority of patients were treated with SPRYCEL tablets 60 mg/m^2 once daily (maximum dose of 100 mg once daily for patients with high BSA). Patients were treated until disease progression or unacceptable toxicity. The safety profile of dasatinib in pediatric subjects was comparable to that reported in studies in adult subjects with chronic phase CML. Monitor bone growth and development in pediatric patients *[see Warnings and Precautions (5.10]*.

8.5 Geriatric Use

No differences in confirmed Complete Cytogenetic Response (cCCyR) and MMR were observed between older and younger patients. Of the 2712 patients in clinical studies of SPRYCEL, 617 (23%) were 65 years of age and older, and 123 (5%) were 75 years of age and older. While the safety profile of SPRYCEL in the geriatric population was similar to that in the younger population, patients aged 65 years and older are more likely to experience the commonly reported adverse reactions of fatigue, pleural effusion, diarrhea, dyspnea, cough, lower gastrointestinal hemorrhage, and appetite disturbance, and more likely to experience the less frequently reported adverse reactions of abdominal distention, dizziness, pericardial effusion, congestive heart failure, hypertension, pulmonary edema, and weight decrease, and should be monitored closely.

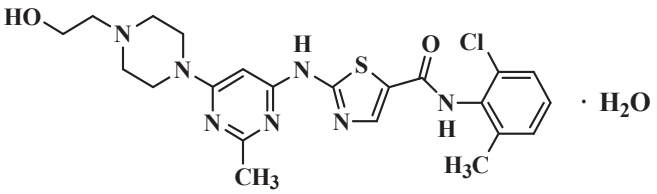
10 OVERDOSAGE

Experience with overdose of SPRYCEL in clinical studies is limited to isolated cases. The highest overdosage of 280 mg per day for 1 week was reported in two patients and both developed severe myelosuppression and bleeding. Since SPRYCEL is associated with severe myelosuppression *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*, monitor patients who ingest more than the recommended dosage closely for myelosuppression and give appropriate supportive treatment.

Acute overdose in animals was associated with cardiotoxicity. Evidence of cardiotoxicity included ventricular necrosis and valvular/ventricular/atrial hemorrhage at single doses ≥100 mg/kg (600 mg/m^2) in rodents. There was a tendency for increased systolic and diastolic blood pressure in monkeys at single doses ≥10 mg/kg (120 mg/m^2).

11 DESCRIPTION

SPRYCEL (dasatinib) is a kinase inhibitor. The chemical name for dasatinib is N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide, monohydrate. The molecular formula is $C_{22}H_{26}ClN_7O_2S \bullet H_2O$, which corresponds to a formula weight of 506.02 (monohydrate). The anhydrous free base has a molecular weight of 488.01. Dasatinib has the following chemical structure:



Dasatinib is a white to off-white powder. The drug substance is insoluble in water and slightly soluble in ethanol and methanol.

SPRYCEL tablets are white to off-white, biconvex, film-coated tablets containing dasatinib, with the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The tablet coating consists of hypromellose, titanium dioxide, and polyethylene glycol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dasatinib, at nanomolar concentrations, inhibits the following kinases: BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, EPHA2, and PDGFRβ. Based on modeling studies, dasatinib is predicted to bind to multiple conformations of the ABL kinase.

In vitro, dasatinib was active in leukemic cell lines representing variants of imatinib mesylate-sensitive and resistant disease. Dasatinib inhibited the growth of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) cell lines overexpressing BCR-ABL. Under the conditions of the assays, dasatinib could overcome imatinib resistance resulting from BCR-ABL kinase domain mutations, activation of alternate signaling pathways involving the SRC family kinases (LYN, HCK), and multi-drug resistance gene overexpression.

12.2 Pharmacodynamics

Cardiac Electrophysiology

Of 2440 patients treated with SPRYCEL at all doses tested in clinical trials, 16 patients (<1%) had QTc prolongation reported as an adverse reaction. Twenty-two patients (1%) experienced a QTcF > 500 ms. In 865 patients with leukemia treated with SPRYCEL 70 mg BID in five Phase 2 studies,

the maximum mean changes in QTcF (90% upper bound CI) from baseline ranged from 7 ms to 13.4 ms.

An analysis of the data from five Phase 2 studies in patients (70 mg BID) and a Phase 1 study in healthy subjects (100 mg single dose) suggests that there is a maximum increase of 3 to 6 milliseconds in Fridericia corrected QTc interval from baseline for subjects receiving therapeutic doses of dasatinib, with associated upper 95% confidence intervals <10 msec.

12.3 Pharmacokinetics

The pharmacokinetics of dasatinib exhibits dose proportional increases in AUC and linear elimination characteristics over the dose range of 15 mg/day (0.15 times the lowest approved recommended dose) to 240 mg/day (1.7 times the highest approved recommended dose).

At 100 mg QD, the maximum concentration at steady state (C_{max}) is 82.2 ng/mL (CV% 69%), area under the plasma drug concentration time curve (AUC) is 397 ng/mL*hr (CV% 55%). The clearance of dasatinib is found to be time-invariant.

Absorption

The maximum plasma concentrations (C_{max}) of dasatinib are observed between 0.5 hours and 6 hours (T_{max}) following oral administration.

Food Effect

A high-fat meal increased the mean AUC of dasatinib following a single dose of 100 mg by 14%. The total calorie content of the high-fat meal was 985 kcal. The calories derived from fat, carbohydrates, and protein were 52%, 34%, and 14% for the high-fat meal.

Distribution

The apparent volume of distribution is 2505 L (CV% 93%).

Binding of dasatinib to human plasma proteins in vitro was approximately 96% and of its active metabolite was 93%, with no concentration dependence over the range of 100 ng/mL to 500 ng/mL.

Dasatinib is a P-gp substrate in vitro.

Elimination

The mean terminal half-life of dasatinib is 3 hours to 5 hours. The mean apparent oral clearance is 363.8 L/hr (CV% 81.3%).

Metabolism

Dasatinib is metabolized in humans, primarily by CYP3A4. CYP3A4 is the primary enzyme responsible for the formation of the active metabolite. Flavin-containing monooxygenase 3 (FMO-3) and uridine diphosphate-glucuronosyltransferase (UGT) enzymes are also involved in the formation of dasatinib metabolites.

The exposure of the active metabolite, which is equipotent to dasatinib, represents approximately 5% of the AUC of dasatinib. The active metabolite of dasatinib is unlikely to play a major role in the observed pharmacology of the drug. Dasatinib also has several other inactive oxidative metabolites.

Excretion

Elimination is primarily via the feces. Following a single radiolabeled dose of oral dasatinib, 4% of the administered radioactivity was recovered in the urine and 85% in the feces within 10 days. Unchanged dasatinib accounted for 0.1% of the administered dose in the urine and 19% of the administered dose in the feces with the remainder of the dose being metabolites.

Specific Populations

Age (15 to 86 years old), sex, and renal impairment (creatinine clearance 21.6 mL/min to 342.3 mL/min as estimated by Cockcroft Gault) have no clinically relevant effect on the pharmacokinetics of dasatinib.

Pediatric Patients

The pharmacokinetics of dasatinib were evaluated in 43 pediatric patients with leukemia or solid tumors at oral doses ranging from 60 mg/m^2 to 120 mg/m^2 once daily, taken with or without food. The pharmacokinetics showed dose proportionality with a dose-related increase in exposure. The mean T_{max} was observed between 0.5 hours and 6 hours and the mean half-life was 2 hours to 5 hours. The geometric mean (CV%) of body weight normalized clearance in these 43 pediatric patients is 5.98 (41.5%) L/h/kg. In pediatric patients with a dosing regimen of 60 mg/m^2, the model simulated geometric mean (CV%) steady-state plasma average concentrations of dasatinib were 14.7 (64.6%) ng/mL (for 2 to <6 years old), 16.3 (97.5%) ng/mL (for 6 to <12 years old), and 18.2 (67.7%) ng/mL (for 12 years and older) *[see Dosage and Administration (2.2)]*. Dasatinib clearance and volume of distribution change with body weight in pediatric patients. Dasatinib has not been studied in patients < 1 year old.

Patients with Hepatic Impairment

Compared to subjects with normal liver function, patients with moderate hepatic impairment (Child Pugh B) had decreases in mean C_{max} by 47% and mean AUC by 8%. Patients with severe hepatic impairment (Child Pugh C) had decreases in mean C_{max} by 43% and in mean AUC by 28% compared to the subjects with normal liver function.

Drug Interaction Studies

Cytochrome P450 Enzymes

The coadministration of ketoconazole (strong CYP3A4 inhibitor) twice daily increased the mean C_{max} of dasatinib by 4-fold and the mean AUC of dasatinib by 5-fold following a single oral dose of 20 mg.

The coadministration of rifampin (strong CYP3A4 inducer) once daily decreased the mean C_{max} of dasatinib by 81% and the mean AUC of dasatinib by 82%.

Dasatinib is a time-dependent inhibitor of CYP3A4. Dasatinib does not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, or 2E1. Dasatinib does not induce CYP enzymes.

Gastric Acid Reducing Agents

The administration of 30 mL of aluminum hydroxide/magnesium hydroxide 2 hours prior to a single dose of SPRYCEL was associated with no relevant change in the mean AUC of dasatinib; however, the mean C_{max} of dasatinib was increased by 26%.

The simultaneous administration of 30 mL of aluminum hydroxide/magnesium hydroxide with a single dose of SPRYCEL was associated with a 55% reduction in the mean AUC of dasatinib and a 58% reduction in the mean C_{max} of dasatinib.

The administration of a single dose of SPRYCEL 10 hours following famotidine (H_2 antagonist) reduced the mean AUC of dasatinib by 61% and the mean C_{max} of dasatinib by 63%.

The administration of a single 100 mg dose of SPRYCEL 22 hours following a 40 mg dose of omeprazole (proton pump inhibitor) at steady state reduced the mean AUC of dasatinib by 43% and the mean C_{max} of dasatinib by 42%.

Transporters

Dasatinib is a not an inhibitor of P-gp in vitro.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study, rats were administered oral doses of dasatinib at 0.3, 1, and 3 mg/kg/day. The highest dose resulted in a plasma drug exposure (AUC) level approximately 60% of the human exposure at 100 mg once daily. Dasatinib induced a statistically significant increase in the combined incidence of squamous cell carcinomas and papillomas in the uterus and cervix of high-dose females and prostate adenoma in low-dose males.

Dasatinib was clastogenic when tested *in vitro* in Chinese hamster ovary cells, with and without metabolic activation. Dasatinib was not mutagenic when tested in an *in vitro* bacterial cell assay (Ames test) and was not genotoxic in an *in vivo* rat micronucleus study.

Dasatinib did not affect mating or fertility in male and female rats at plasma drug exposure (AUC) similar to the human exposure at 100 mg daily. In repeat dose studies, administration of dasatinib resulted in reduced size and secretion of seminal vesicles, and immature prostate, seminal vesicle, and testis. The administration of dasatinib resulted in uterine inflammation and mineralization in monkeys, and cystic ovaries and ovarian hypertrophy in rodents.

14 CLINICAL STUDIES

14.1 Newly Diagnosed Chronic Phase CML in Adults

DASISION (Dasatinib vs Imatinib Study in Treatment-Naive Chronic Myeloid Leukemia Patients) (NCT00481247) was an open-label, multicenter, international, randomized trial conducted in adult patients with newly diagnosed chronic phase CML. A total of 519 patients were randomized to receive either SPRYCEL 100 mg once daily or imatinib 400 mg once daily. Patients with a history of cardiac disease were included in this trial except those who had a myocardial infarction within 6 months, congestive heart failure within 3 months, significant arrhythmias, or QTc prolongation. The primary endpoint was the rate of confirmed complete cytogenetic response (CCyR) within 12 months. Confirmed CCyR was defined as a CCyR noted on two consecutive occasions (at least 28 days apart).

Median age was 46 years in the SPRYCEL group and 49 years in the imatinib groups, with 10% and 11% of patients ≥65 years of age, respectively. There were slightly more male than female

patients in both groups (59% vs 41%). Fifty-three percent of all patients were Caucasian and 39% were Asian. At baseline, the distribution of Hasford scores was similar in the SPRYCEL and imatinib treatment groups (low risk: 33% and 34%; intermediate risk: 48% and 47%; high risk: 19% and 19%, respectively). With a minimum of 12 months follow-up, 85% of patients randomized to SPRYCEL and 81% of patients randomized to imatinib were still on study.

With a minimum of 24 months follow-up, 77% of patients randomized to SPRYCEL and 75% of patients randomized to imatinib were still on study and with a minimum of 60 months follow-up, 61% and 62% of patients, respectively, were still on treatment at the time of study closure.

Efficacy results are summarized in Table 14.

Table 13: Efficacy Results in a Randomized Newly Diagnosed Chronic Phase CML Trial

	SPRYCEL (n=259)		Imatinib (n=260)
Confirmed CCyR[a]			
Within 12 months (95% CI)	76.8% (71.2–81.8)		66.2% (60.1–71.9)
P-value		0.007*	
Major Molecular Response[b]			
12 months (95% CI)	52.1% (45.9–58.3)		33.8% (28.1–39.9)
P-value		<0.0001	
60 months (95% CI)	76.4% (70.8–81.5)		64.2% (58.1–70.1)

[a] Confirmed CCyR is defined as a CCyR noted on two consecutive occasions at least 28 days apart.

[b] Major molecular response (at any time) was defined as BCR-ABL ratios ≤0.1% by RQ-PCR in peripheral blood samples standardized on the International scale. These are cumulative rates representing minimum follow up for the time frame specified.

* Adjusted for Hasford score and indicated statistical significance at a pre-defined nominal level of significance.

CI = confidence interval.

The confirmed CCyR within 24, 36, and 60 months for SPRYCEL versus imatinib arms were 80% versus 74%, 83% versus 77%, and 83% versus 79%, respectively. The MMR at 24 and 36 months for SPRYCEL versus imatinib arms were 65% versus 50% and 69% versus 56%, respectively.

After 60 months follow-up, median time to confirmed CCyR was 3.1 months in 215 SPRYCEL responders and 5.8 months in 204 imatinib responders. Median time to MMR after 60 months follow-up was 9.3 months in 198 SPRYCEL responders and 15.0 months in 167 imatinib responders.

At 60 months, 8 patients (3%) on the dasatinib arm progressed to either accelerated phase or blast crisis while 15 patients (6%) on the imatinib arm progressed to either accelerated phase or blast crisis.

The estimated 60-month survival rates for SPRYCEL- and imatinib-treated patients were 90.9% (CI: 86.6%–93.8%) and 89.6% (CI: 85.2%–92.8%), respectively. Based on data 5 years after the last patient was enrolled in the trial, 83% and 77% of patients were known to be alive in the

dasatinib and imatinib treatment groups, respectively, 10% were known to have died in both treatment groups, and 7% and 13% had unknown survival status in the dasatinib and imatinib treatment groups, respectively.

At 60 months follow-up in the SPRYCEL arm, the rate of MMR at any time in each risk group determined by Hasford score was 90% (low risk), 71% (intermediate risk) and 67% (high risk). In the imatinib arm, the rate of MMR at any time in each risk group determined by Hasford score was 69% (low risk), 65% (intermediate risk), and 54% (high risk).

BCR-ABL sequencing was performed on blood samples from patients in the newly diagnosed trial who discontinued dasatinib or imatinib therapy. Among dasatinib-treated patients the mutations detected were T315I, F317I/L, and V299L.

Dasatinib does not appear to be active against the T315I mutation, based on *in vitro* data.

14.2 Imatinib-Resistant or -Intolerant CML or Ph+ ALL in Adults

The efficacy and safety of SPRYCEL were investigated in adult patients with CML or Ph+ ALL whose disease was resistant to or who were intolerant to imatinib: 1158 patients had chronic phase CML, 858 patients had accelerated phase, myeloid blast phase, or lymphoid blast phase CML, and 130 patients had Ph+ ALL. In a clinical trial in chronic phase CML, resistance to imatinib was defined as failure to achieve a complete hematologic response (CHR; after 3 months), major cytogenetic response (MCyR; after 6 months), or complete cytogenetic response (CCyR; after 12 months); or loss of a previous molecular response (with concurrent ≥10% increase in Ph+ metaphases), cytogenetic response, or hematologic response. Imatinib intolerance was defined as inability to tolerate 400 mg or more of imatinib per day or discontinuation of imatinib because of toxicity.

Results described below are based on a minimum of 2 years follow-up after the start of SPRYCEL therapy in patients with a median time from initial diagnosis of approximately 5 years. Across all studies, 48% of patients were women, 81% were white, 15% were black or Asian, 25% were 65 years of age or older, and 5% were 75 years of age or older. Most patients had long disease histories with extensive prior treatment, including imatinib, cytotoxic chemotherapy, interferon, and stem cell transplant. Overall, 80% of patients had imatinib-resistant disease and 20% of patients were intolerant to imatinib. The maximum imatinib dose had been 400–600 mg/day in about 60% of the patients and >600 mg/day in 40% of the patients.

The primary efficacy endpoint in chronic phase CML was MCyR, defined as elimination (CCyR) or substantial diminution (by at least 65%, partial cytogenetic response) of Ph+ hematopoietic cells. The primary efficacy endpoint in accelerated phase, myeloid blast phase, lymphoid blast phase CML, and Ph+ ALL was major hematologic response (MaHR), defined as either a CHR or no evidence of leukemia (NEL).

Chronic Phase CML

Dose-Optimization Trial: A randomized, open-label trial (NCT00123474) was conducted in adult patients with chronic phase CML to evaluate the efficacy and safety of SPRYCEL administered once daily compared with SPRYCEL administered twice daily. Patients with significant cardiac

diseases, including myocardial infarction within 6 months, congestive heart failure within 3 months, significant arrhythmias, or QTc prolongation were excluded from the trial. The primary efficacy endpoint was MCyR in patients with imatinib-resistant CML. A total of 670 patients, of whom 497 had imatinib-resistant disease, were randomized to the SPRYCEL 100 mg once-daily, 140 mg once-daily, 50 mg twice-daily, or 70 mg twice-daily group. Median duration of treatment was 22 months.

Efficacy was achieved across all SPRYCEL treatment groups with the once-daily schedule demonstrating comparable efficacy (non-inferiority) to the twice-daily schedule on the primary efficacy endpoint (difference in MCyR 1.9%; 95% CI [−6.8%–10.6%]); however, the 100-mg once-daily regimen demonstrated improved safety and tolerability.

Efficacy results are presented in Tables 15 and 16 for adult patients with chronic phase CML who received the recommended starting dose of 100 mg once daily.

Table 14: Efficacy of SPRYCEL in Adult Patients with Imatinib-Resistant or -Intolerant Chronic Phase CML (minimum of 24 months follow-up)

All Patients	100 mg Once Daily (n=167)
Hematologic Response Rate % (95% CI)	
CHR[a]	92% (86–95)
Cytogenetic Response Rate % (95% CI)	
MCyR[b]	63% (56–71)
CCyR	50% (42–58)

[a] CHR (response confirmed after 4 weeks): WBC ≤ institutional ULN, platelets <450,000/mm^3, no blasts or promyelocytes in peripheral blood, <5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood <20%, and no extramedullary involvement.

[b] MCyR combines both complete (0% Ph+ metaphases) and partial (>0%–35%) responses.

Table 15: Long-Term MMR of SPRYCEL in the Dose Optimization Trial: Adult Patients with Imatinib-Resistant or -Intolerant Chronic Phase CML[a]

	Minimum Follow-up Period		
	2 Years	5 Years	7 Years
Major Molecular Response[b] % (n/N)			
All Patients Randomized	34% (57/167)	43% (71/167)	44% (73/167)
Imatinib-Resistant Patients	33% (41/124)	40% (50/124)	41% (51/124)
Imatinib-Intolerant Patients	37% (16/43)	49% (21/43)	51% (22/43)

[a] Results reported in recommended starting dose of 100 mg once daily.

[b] Major molecular response criteria: Defined as BCR-ABL/control transcripts ≤0.1% by RQ-PCR in peripheral blood samples.

Based on data 7 years after the last patient was enrolled in the trial, 44% were known to be alive, 31% were known to have died, and 25% had an unknown survival status.

By 7 years, transformation to either accelerated or blast phase occurred in nine patients on treatment in the 100 mg once-daily treatment group.

Advanced Phase CML and Ph+ ALL

Dose-Optimization Trial: One randomized open-label trial (NCT00123487) was conducted in patients with advanced phase CML (accelerated phase CML, myeloid blast phase CML, or lymphoid blast phase CML) to evaluate the efficacy and safety of SPRYCEL administered once daily compared with SPRYCEL administered twice daily. The primary efficacy endpoint was MaHR. A total of 611 patients were randomized to either the SPRYCEL 140 mg once-daily or 70 mg twice-daily group. Median duration of treatment was approximately 6 months for both treatment groups. The once-daily schedule demonstrated comparable efficacy (non-inferiority) to the twice-daily schedule on the primary efficacy endpoint; however, the 140-mg once-daily regimen demonstrated improved safety and tolerability.

Response rates for patients in the 140 mg once-daily group are presented in Table 17.

Table 16: Efficacy of SPRYCEL in Imatinib-Resistant or -Intolerant Advanced Phase CML and Ph+ ALL (2-Year Results)

	140 mg Once Daily			
	Accelerated (n=158)	**Myeloid Blast (n=75)**	**Lymphoid Blast (n=33)**	**Ph+ ALL (n=40)**
MaHR[a] (95% CI)	66% (59–74)	28% (18–40)	42% (26–61)	38% (23–54)
CHR[a] (95% CI)	47% (40–56)	17% (10–28)	21% (9–39)	33% (19–49)
NEL[a] (95% CI)	19% (13–26)	11% (5–20)	21% (9–39)	5% (1–17)
MCyR[b] (95% CI)	39% (31–47)	28% (18–40)	52% (34–69)	70% (54–83)
CCyR (95% CI)	32% (25–40)	17% (10–28)	39% (23–58)	50% (34–66)

[a] Hematologic response criteria (all responses confirmed after 4 weeks): Major hematologic response: (MaHR) = complete hematologic response (CHR) + no evidence of leukemia (NEL).
CHR: WBC ≤ institutional ULN, ANC ≥1000/mm^3, platelets ≥100,000/mm^3, no blasts or promyelocytes in peripheral blood, bone marrow blasts ≤5%, <5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood <20%, and no extramedullary involvement.
NEL: same criteria as for CHR but ANC ≥500/mm^3 and <1000/mm^3, or platelets ≥20,000/mm^3 and ≤100,000/mm^3.

[b] MCyR combines both complete (0% Ph+ metaphases) and partial (>0%–35%) responses.

CI = confidence interval ULN = upper limit of normal range.

In the SPRYCEL 140 mg once-daily group, the median time to MaHR was 1.9 months (min-max: 0.7-14.5) for patients with accelerated phase CML, 1.9 months (min-max: 0.9-6.2) for patients with myeloid blast phase CML, and 1.8 months (min-max: 0.9-2.8) for patients with lymphoid blast phase CML.

In patients with myeloid blast phase CML, the median duration of MaHR was 8.1 months (min-max: 2.7-21.1) and 9.0 (min-max: 1.8-23.1) months for the 140 mg once-daily group and the 70 mg twice-daily group, respectively. In patients with lymphoid blast phase CML, the median duration of MaHR was 4.7 months (min-max: 3.0-9.0) and 7.9 months (min-max: 1.6-22.1) for the 140 mg once-daily group and the 70 mg twice-daily group, respectively. In patients with Ph+ ALL who were treated with SPRYCEL 140 mg once-daily, the median duration of MaHR was 4.6 months (min-max: 1.4-10.2). The medians of progression-free survival for patients with Ph+ ALL treated with SPRYCEL 140 mg once-daily and 70 mg twice-daily were 4.0 months (min-max: 0.4-11.1) and 3.1 months (min-max: 0.3-20.8), respectively.

14.3 CML in Pediatric Patients

The efficacy of SPRYCEL in pediatric patients was evaluated in two pediatric studies of 97 patients with chronic phase CML. Among 97 patients with chronic phase CML treated in two pediatric studies, an open-label, non-randomized dose-ranging trial (NCT00306202) and an open-label, non-randomized, single-arm trial (NCT00777036), 51 patients (exclusively from the single-arm trial) had newly diagnosed with chronic phase CML and 46 patients (17 from the dose-ranging trial and 29 from the single-arm trial) were resistant or intolerant to previous treatment with imatinib. Ninety-one of the 97 pediatric patients were treated with SPRYCEL tablets 60 mg/m^2 once daily (maximum dose of 100 mg once daily for patients with high BSA). Patients were treated until disease progression or unacceptable toxicity.

Baseline demographic characteristics of the 46 imatinib resistant or intolerant patients were: median age 13.5 years (range 2 to 20 years), 78.3% White, 15.2% Asian, 4.4% Black, 2.2% other, and 52% female. Baseline characteristics of the 51 newly diagnosed patients were: median age 12.8 years (range 1.9 to 17.8 years), 60.8% White, 31.4% Asian, 5.9% Black, 2% Other, and 49% female.

Median duration of follow-up was 5.2 years (range 0.5 to 9.3 years) for the imatinib resistant or intolerant patients and 4.5 years (range 1.3 to 6.4 years) for the newly diagnosed patients, respectively. Efficacy results for the two pediatric studies are summarized in Table 18.

Table 18 shows increasing trend for response for CCyR, MCyR, and MMR across time (3 months to 24 months). The increasing trend in response for all three endpoints is seen in both the newly diagnosed and imatinib resistant or intolerant patients.

Table 17: Efficacy of SPRYCEL in Pediatric Patients with CP-CML Cumulative Response Over Time by Minimum Follow-Up Period

	3 months	6 months	12 months	24 months
CCyR				
(95% CI)				
Newly diagnosed (N = 51)[a]	43.1% (29.3, 57.8)	66.7% (52.1, 79.2)	96.1% (86.5, 99.5)	96.1% (86.5, 99.5)
Prior imatinib (N = 46)[b]	45.7% (30.9, 61.0)	71.7% (56.5, 84.0)	78.3% (63.6, 89.1)	82.6% (68.6, 92.2)
MCyR				
(95% CI)				
Newly diagnosed (N = 51)[a]	60.8% (46.1, 74.2)	90.2% (78.6, 96.7)	98.0% (89.6, 100)	98.0% (89.6, 100)
Prior imatinib (N = 46)[b]	60.9% (45.4, 74.9)	82.6% (68.6, 92.2)	89.1% (76.4, 96.4)	89.1% (76.4, 96.4)
MMR				
(95% CI)				
Newly diagnosed (N = 51)[a]	7.8% (2.2, 18.9)	31.4% (19.1, 45.9)	56.9% (42.2, 70.7)	74.5% (60.4, 85.7)
Prior imatinib (N = 46)[b]	15.2% (6.3, 28.9)	26.1% (14.3, 41.1)	39.1% (25.1, 54.6)	52.2% (36.9, 67.1)

[a]Patients from pediatric study of newly diagnosed CP-CML receiving oral tablet formulation
[b]Patients from pediatric studies of imatinib-resistant or -intolerant CP-CML receiving oral tablet formulation

With a median follow-up of 4.5 years in newly diagnosed patients, the median durations of CCyR, MCyR, MMR could not be estimated as more than half of the responding patients had not progressed at the time of data cut-off. Range of duration of response was (2.5+ to 66.5+ months for CCyR), (1.4 to 66.5+ months for MCyR), and (5.4+ to 72.5+ months for subjects who achieved MMR by month 24 and 0.03+ to 72.5+ months for subjects who achieved MMR at any time), where '+' indicates a censored observation.

With a median follow-up of 5.2 years in imatinib-resistant or - intolerant patients, the median durations of CCyR, MCyR, and MMR could not be estimated as more than half the responding patients had not progressed at the time of data cut-off. Range of duration of response was (2.4 to 86.9+ months for CCyR), (2.4 to 86.9+ months for MCyR), and (2.6+ to 73.6+ months for MMR), where '+' indicates a censored observation.

The median time to response for MCyR was 2.9 months (95% CI: 2.8 months, 3.5 months) in the pooled imatinib-resistant/intolerant CP-CML patients. The median time to response for CCyR was 3.3 months (95% CI: 2.8 months, 4.7 months) in the pooled imatinib-resistant/intolerant CP-CML patients. The median time to response for MMR was 8.3 months (95% CI: 5.0 months, 11.8 months) in the pooled imatinib- resistant/intolerant CP-CML patients.

The median time to response for MCyR was 3.0 months (95% CI: 2.8 months, 4.3 months) in the newly diagnosed treatment naïve CP-CML patients. The median time to response for CCyR was 5.5 months (95% CI: 3.0 months, 5.7 months) in the newly diagnosed treatment-naïve CP-CML patients. The median time to response for MMR was 8.9 months (95% CI: 6.2 months, 11.7 months) in the newly diagnosed treatment-naïve CP-CML patients.

In the Phase II pediatric study, 1 newly diagnosed patient and 2 imatinib-resistant or -intolerant patients progressed to blast phase CML.

15 REFERENCES

1. http://www.osha.gov/SLTC/hazardousdrugs/index.html

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

SPRYCEL® (dasatinib) tablets are available as described in Table 19.

Table 18: SPRYCEL Trade Presentations

NDC Number	Strength	Description	Tablets per Bottle
0003-0527-11	20 mg	white to off-white, biconvex, round, film-coated tablet with “BMS” debossed on one side and “527” on the other side	60
0003-0528-11	50 mg	white to off-white, biconvex, oval, film-coated tablet with “BMS” debossed on one side and “528” on the other side	60
0003-0524-11	70 mg	white to off-white, biconvex, round, film-coated tablet with “BMS” debossed on one side and “524” on the other side	60
0003-0855-22	80 mg	white to off-white, biconvex, triangle, film-coated tablet with “BMS” and “80” (BMS over 80) debossed on one side and “855” on the other side	30
0003-0852-22	100 mg	white to off-white, biconvex, oval, film-coated tablet with “BMS 100” debossed on one side and “852” on the other side	30
0003-0857-22	140 mg	white to off-white, biconvex, round, film-coated tablet with “BMS” and “140” (BMS over 140) debossed on one side and “857” on the other side	30

16.2 Storage

SPRYCEL tablets should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

16.3 Handling and Disposal

SPRYCEL is an antineoplastic product. Follow special handling and disposal procedures.[1]

Personnel who are pregnant should avoid exposure to crushed or broken tablets.

SPRYCEL tablets consist of a core tablet, surrounded by a film coating to prevent exposure of healthcare professionals to the active substance. The use of latex or nitrile gloves for appropriate disposal when handling tablets that are inadvertently crushed or broken is recommended, to minimize the risk of dermal exposure.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Bleeding

Patients should be informed of the possibility of serious bleeding and to report immediately any signs or symptoms suggestive of hemorrhage (unusual bleeding or easy bruising) *[see Warnings and Precautions (5.2)]*.

Myelosuppression

Patients should be informed of the possibility of developing low blood cell counts; they should be instructed to report immediately should fever develop, particularly in association with any suggestion of infection *[see Warnings and Precautions (5.1)]*.

Fluid Retention

Patients should be informed of the possibility of developing fluid retention (swelling, weight gain, dry cough, chest pain on respiration, or shortness of breath) and advised to seek medical attention promptly if those symptoms arise *[see Warnings and Precautions (5.3)]*.

Pulmonary Arterial Hypertension

Patients should be informed of the possibility of developing pulmonary arterial hypertension (dyspnea, fatigue, hypoxia, and fluid retention) and advised to seek medical attention promptly if those symptoms arise *[see Warnings and Precautions (5.5)]*.

Tumor Lysis Syndrome

Patients should be informed to immediately report and seek medical attention for any symptoms such as nausea, vomiting, weakness, edema, shortness of breath, muscle cramps, and seizures, which may indicate tumor lysis syndrome *[see Warnings and Precautions (5.8)]*.

Growth and Development in Pediatric Patients

Pediatric patients and their caregivers should be informed of the possibility of developing bone growth abnormalities, bone pain, or gynecomastia and advised to seek medical attention promptly if those symptoms arise *[see Warnings and Precautions (5.10)]*.

Embryo-Fetal Toxicity

- Advise pregnant women of the potential risk to a fetus *[see Warnings and Precautions (5.9) and Use in Specific Populations (8.1)]*.
- Advise females of reproductive potential to avoid pregnancy, which may include use of effective contraception during treatment with SPRYCEL and for 30 days after the final dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking SPRYCEL *[see Warnings and Precautions (5.9) and Use in Specific Populations (8.1, 8.3)]*.

Lactation

- Advise women that breastfeeding is not recommended during treatment with SPRYCEL and for 2 weeks after the final dose *[see Use in Specific Populations (8.2)]*.

Gastrointestinal Complaints

Patients should be informed that they may experience nausea, vomiting, or diarrhea with SPRYCEL. If these symptoms are bothersome or persistent, they should seek medical attention.

Advise patients using antacids to avoid taking SPRYCEL and antacids less than 2 hours apart *[see Drug Interactions (7.1)]*.

Pain

Patients should be informed that they may experience headache or musculoskeletal pain with SPRYCEL. If these symptoms are bothersome or persistent, they should seek medical attention.

Fatigue

Patients should be informed that they may experience fatigue with SPRYCEL. If this symptom is bothersome or persistent, they should seek medical attention.

Rash

Patients should be informed that they may experience skin rash with SPRYCEL. If this symptom is bothersome or persistent, they should seek medical attention.

Lactose

Patients should be informed that SPRYCEL contains 135 mg of lactose monohydrate in a 100-mg daily dose and 189 mg of lactose monohydrate in a 140-mg daily dose.

Missed Dose

If the patient misses a dose of SPRYCEL, the patient should take the next scheduled dose at its regular time. The patient should not take two doses at the same time.

Distributed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

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PATIENT INFORMATION
SPRYCEL® (Spry-sell)
(dasatinib)
tablets

What is SPRYCEL?

SPRYCEL® is a prescription medicine used to treat:

- adults with newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase.
- adults with Ph+ CML who no longer benefit from, or did not tolerate, other treatment, including Gleevec® (imatinib mesylate).
- adults with Ph+ acute lymphoblastic leukemia (Ph+ ALL) who no longer benefit from, or did not tolerate, other treatment.
- children with Ph+ CML in chronic phase.

Before taking SPRYCEL, tell your healthcare provider about all of your medical conditions, including if you:

- have problems with your immune system
- have heart problems, including a condition called congenital long QT syndrome
- have low potassium or low magnesium levels in your blood
- are lactose (milk sugar) intolerant
- are pregnant or plan to become pregnant. SPRYCEL can harm your unborn baby. If you are able to become pregnant, you should use effective birth control during treatment and for 30 days after your final dose of SPRYCEL. Talk to your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with SPRYCEL.
- are breastfeeding or plan to breastfeed. It is not known if SPRYCEL passes into your breast milk. You should not breastfeed during treatment and for 2 weeks after your final dose of SPRYCEL.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, antacids, and herbal supplements**. If you take an antacid medicine, take it 2 hours before or 2 hours after your dose of SPRYCEL.**

How should I take SPRYCEL?

- Take SPRYCEL exactly as your healthcare provider tells you to take it.
- Your healthcare provider may change your dose of SPRYCEL or temporarily stop treatment with SPRYCEL. **Do not change your dose or stop taking SPRYCEL without first talking to your healthcare provider.**
- Take SPRYCEL one (1) time a day.
- Take SPRYCEL with or without food, either in the morning or in the evening.
- Swallow SPRYCEL tablets whole. Do not crush, cut or chew the tablets.
- You should not drink grapefruit juice during treatment with SPRYCEL.
- If you miss a dose of SPRYCEL, take your next scheduled dose at your regular time. Do not take two doses at the same time.
- If you take too much SPRYCEL, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of SPRYCEL?

SPRYCEL may cause serious side effects, including:

- **Low blood cell counts.** Low blood cell counts are common with SPRYCEL and can be severe, including low red blood cell counts (anemia), low white blood cell counts (neutropenia), and low platelet counts (thrombocytopenia). Your healthcare provider will do blood tests to check your blood cell counts regularly during your treatment with

SPRYCEL. Call your healthcare provider right away if you have a fever or any signs of an infection during treatment with SPRYCEL.

- **Bleeding problems.** Bleeding problems are common with SPRYCEL. Sometimes these bleeding problems can be serious and lead to death. Call your healthcare provider right away if you have:
  - unusual bleeding or bruising of your skin
  - bright red or dark tar-like stools
  - decreased alertness, headache, or change in speech
- **Your body may hold too much fluid (fluid retention).** Fluid retention is common with SPRYCEL and can sometimes be severe. In severe cases, fluid may build up in the lining of your lungs, the sac around your heart, or your stomach cavity. Call your healthcare provider right away if you get any of these symptoms during treatment with SPRYCEL:
  - swelling all over your body
  - weight gain
  - shortness of breath, especially if this happens with low levels of physical activity or at rest
  - dry cough
  - chest pain when taking a deep breath
- **Heart problems.** SPRYCEL may cause an abnormal heart rate, heart problems, or a heart attack. Your healthcare provider will monitor the potassium and magnesium levels in your blood, and your heart function.
- **Pulmonary Arterial Hypertension (PAH).** SPRYCEL may cause high blood pressure in the vessels of your lungs. PAH may happen at any time during your treatment with SPRYCEL. Your healthcare provider should check your heart and lungs before and during treatment with SPRYCEL. Call your healthcare provider right away if you have shortness of breath, tiredness, or swelling all over your body (fluid retention).
- **Severe skin reactions.** SPRYCEL may cause skin reactions that can sometimes be severe. Get medical help right away if you get a skin reaction with fever, sore mouth or throat, or blistering or peeling of your skin or in the mouth.
- **Tumor Lysis Syndrome (TLS).** TLS is caused by a fast breakdown of cancer cells. TLS can cause you to have kidney failure and the need for dialysis treatment, and an abnormal heartbeat. Your healthcare provider may do blood tests to check you for TLS.
- **Slowing of growth and development in children.** Effects on bone growth and development in children with chronic phase CML have happened with SPRYCEL and can sometimes be severe.

The most common side effects of SPRYCEL in adults include:

- diarrhea
- headache
- skin rash
- shortness of breath
- tiredness
- nausea
- muscle pain

The most common side effects of SPRYCEL in children include:

- headache
- nausea
- pain in hands or feet (extremities)
- diarrhea
- skin rash
- stomach (abdomen) pain

SPRYCEL may cause fertility problems in males and females. Talk to your healthcare provider if this is a concern for you.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of SPRYCEL.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store SPRYCEL?

- Store SPRYCEL at room temperature between 68°F to 77°F (20°C to 25°C).
- Ask your healthcare provider or pharmacist about the right way to throw away expired or unused SPRYCEL.
- Wear latex or nitrile gloves when handling tablets that have accidentally been crushed or broken.
- Females who are pregnant should not handle crushed or broken SPRYCEL tablets.

Keep SPRYCEL and all medicines out of the reach of children.

General information about the safe and effective use of SPRYCEL.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use SPRYCEL for a condition for which it is not prescribed. Do not give SPRYCEL to other people even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about SPRYCEL that is written for health professionals.

What are the ingredients in SPRYCEL?

Active ingredient: dasatinib

Inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The tablet coating consists of hypromellose, titanium dioxide, and polyethylene glycol.

Distributed by: Bristol-Myers Squibb Company, Princeton, NJ 08543 USA
For more information, go to www.sprycel.com or call 1-800-332-2056.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: November 2017

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21986Orig1s020

DIVISION DIRECTOR MEMO

Division Director Memo to file regarding NDA 21986 s020

NDA 21986 s020 (tablet formulation)

I concur with the review teams regarding the approvability of this application which provides for labeling of pediatric data and an indication for treatment of chronic myelogenous leukemia in pediatric patients with the recommendation for a pediatric dose for CML of 60mg/$m^{2.}$ The clinical trial data used for this indication is primarily from Studies CA180226 and CA 180018. I also concur with the clinical pharmacology recommendation that the tablets should only be swallowed whole and should not be crushed, cut or chewed based on their review of the data and this will be bolded in the label so as to avoid patients being under dosed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN T FARRELL
11/09/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21986Orig1s020

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	8 November 2017
From	Nicole Gormley, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 021986 S-020
Applicant	Bristol-Myers Squibb
Date of Submission	9 May 2017
PDUFA Goal Date	9 Nov 2017
Proprietary Name / **Established (USAN) names**	Sprycel ® dasatinib
Dosage forms / Strength	Tablet 20 mg, 50 mg, 70 mg, 80 mg, 100 mg and 140 mg
Proposed Indication(s)	1. Pediatric Patients with Ph+ CML in chronic phase
Recommended:	Approval

Material Reviewed/Consulted	**Reviewer**
Combined Clinical/Statistical Review	Rachel Ershler, MD; Thomas Ly, Ph.D
Clinical Pharmacology Review	Yuhong Chen, MD, Ph.D; Yuowei Bi, Ph.D; Stacy Shord, Pharm.D; and Justin Earp, Ph.D.
Division of Hematology and Oncology Toxicology	Brenda Gehrke, PhD; Christopher Sheth, PhD
Office of Product Quality	Paresma Patel, PhD; Anamitro Banerjee, PhD
Office of Scientific Investigations	Anthony Orencia, MD, FACP
Division of Medication Error Prevention and Analysis (DMEPA) Consult	Casmir Ogbonna, Pharm.D, MBA, BCPS, BCGP/ Hina Mehta, Pharm. D.
Office of Prescription Drug Promotion	Rachel Conklin, MS, RN; Nisha Patel
Division of Medical Policy Programs (Patient Labeling)	Ruth Lidoshore, PharmD; Rachel Conklin, MS, RN

1. Introduction

(b) (4)[9](efficacy supplement NDA 021986/S-020 (b) (4) (b) (4) NDA 021986 supplement S-020. The proposed indication is Sprycel® (dasatinib) tablets for use in pediatric patients with Philadelphia chromosome positive (Ph+) Chronic Phase Chronic Myeloid Leukemia (CP-CML).

The proposed dosing regimen for this indication was 60 mg/m2 once daily, with weight-tiered dosing proposed for the formulation.

Sprycel® (dasatinib) is tyrosine kinase inhibitor that was first approved in 2006 for the treatment of adults with chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib.

The trials submitted in support of this applications are CA180018, CA180226, and CA180038. The results from CA180018 and CA180226 were considered pivotal to the assessment of safety and efficacy, while data from CA180038 was supportive, as this trial used a different dosing regimen.

2. Background

CML is a myeloproliferative neoplasm characterized by the proliferation of mature granulocytes with fairly normal differentiation. CML is associated with fusion of the Abelson murine leukemia (ABL) gene on chromosome 9 with the breakpoint cluster (BCR) gene on chromosome 22. BCR-ABL is a constitutively active tyrosine kinase that promotes growth and replication.

CML is a common leukemia in the United States, accounting for 15% of all newly diagnosed adult leukemias.[1] It is estimated that there will be 8,950 new cases of CML, and 1,080 deaths from CML in the year 2017.[2]

Nearly half of patients are asymptomatic at diagnosis. The common signs and symptoms, when present, are a result of underlying anemia and splenomegaly and include: fatigue, weight loss, night sweats, and abdominal discomfort. Most patients present in chronic phase, but the disease typically evolves to an accelerated phase, and eventually blast phase in progressive cases.

CML is relatively rare among children and adolescents and constitutes 2% of all leukemias in children younger than 15 years and 9% of all leukemias in adolescents between 15 and 19 years, with an annual incidence of 1 and 2.2 cases per million in these two age groups, respectively.[3] In general, while CML in children arises from the same gene fusion as adults (BCR-ABL1), pediatric CML tends to have a more

aggressive clinical course than adult patients with CML and pediatric patients tend to present with more significant clinical findings, such as larger spleen sizes and higher baseline WBC counts. The proportion of pediatric patients diagnosed with advanced-stage disease (accelerated phase or blast phase) is higher than for adults.[4]

The treatment of CML has changed drastically with the development and approval of tyrosine kinase inhibitors (TKIs). TKIs target the BCR-ABL oncogene, blocking cellular proliferation. In adults, the introduction of the use of TKIs has resulted in a dramatic improvement in clinical outcomes, with an improvement in the 10-year survival rate from 20% to 80-90%[1]. In pediatric patients, TKIs have also resulted in significant improvements in clinical outcomes. However, because of the longer life span of pediatric patients, the morbidity associated with long-term TKI therapy must be weighed against the potential toxicities associated with transplant, the only curative therapy.[5]

Table 1 below (excerpted from Dr. Ershler' s review) lists the drugs approved in the U.S. for the treatment of Pediatric CML.

Table 1. Approved Agents for the treatment of Pediatric CML

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues
Imatinib (Gleevec®)	Newly diagnosed adult and pediatric patients with Ph+ CML in chronic phase	2001: Initial imatinib approval 2011: Approved for pediatric use	340 mg/m^2/day Orally	Results from pivotal Phase 2 study: - CHR at 8 weeks: 78% - CCyR: 65%	- Edema/fluid retention - Cytpenias - CHF/LV dysfunction - Hepatotoxicity - Grade 3/4 hemorrhage - Gastrointestinal perforations - Bullous dermatologic reactions - Renal toxicity - Tumor lysis syndrome

Source: Clinical Review

3. CMC/Device

Refer to the OPQ review by Drs. Patel and Banerjee. The OPQ team recommends approval. There are no labeling changes for the CMC sections with this efficacy supplement.

4. Nonclinical Pharmacology/Toxicology

Refer to the Pharmacology/toxicology review by Dr. Gehrke. No new nonclinical pharmacology/toxicology studies were submitted with this supplement and there were no

proposed changes to the nonclinical sections of the label. The Division of Hematology and Oncology Toxicology determined that this supplement was approvable from a Pharmacology/Toxicology perspective.

5. Clinical Pharmacology/Biopharmaceutics

Source: Clinical Pharmacology Review by Drs. Yuhong Chen, Youwei Bi, Stacy Shord, and Justin Earp.

Dasatinib (SPRYCEL®) is a tyrosine kinase inhibitor. It is approved for the treatment of chronic phase Ph+ CML in adults at a dose of 100 mg QD; and accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL in adults at a dose of 140 mg QD.

The Applicant is seeking the approval of dasatinib for the treatment of pediatric patients with Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. The proposed dose is 60 mg/m^2 once daily (QD) for the commercial tablet. Weight-tiered dosing is proposed.

With regards to the proposed weight-tiered dosing, the Application proposed the following.

Table (b) (4) Dosage of Sprycel (b) (4) for Pediatric Patients

Body Weight (kg)[a]	Daily Dose (mg)
(b) (4)	
at least 45 kg	100 mg

[a] Tablet dosing is not recommended for patients weighing less than 10 kg; (b) (4)

Source: Applicant Initial Prescribing Information

The Applicant proposed that the exposure of weight-tiered dose be considered similar if the geometric mean of simulated steady-state exposure is within 20% of the target exposure. The Clinical pharmacology reviewer agreed that most of the WT-tiered doses proposed by the applicant are expected to provide Cavgss within 20% difference of reference exposure except for the proposed doses at weight category 20 kg to less than 30 kg. A (b) (4) flat dose is expected to produce about 23% lower exposure compared to the reference 60 mg/m2 tablet in pediatric patients weighing between 20 kg to less than 25 kg, whereas a (b) (4) flat dose is expected to produce 18.5% higher exposure compared to the reference tablet in pediatric patients weighing between 25 kg to less than 30kg. The reviewer was concerned that a 23% lower exposure might compromise the efficacy in these patients.

Therefore, the Agency recommended a 60 mg dose for pediatric patients weighing 20 kg to less than 30 kg in the labeling. The Applicant accepted this proposal and the weight-tiered dosing to be included in the PI is below.

Table 3. Dosage of Sprycel for Pediatric Patients

Body Weight (kg)[a]	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

Source: Clinical Pharmacology Review

With regards to the dose/exposure-response relationship for dasatinib, only dose-response analyses were conducted for the 60 mg/m^2 dose, as PK data was not obtained in study CA180026 in the 3a, tablet arm. The relationship was described by a semi-parametric Cox Proportional-Hazards (CPH) model based on data from 51 patients in Cohort 3a (Tablet 60 mg/m^2) and 33 patients in cohort 3b (PFOS 72 mg/m^2) in CA180026.

The Office of Clinical Pharmacology determined that from this sNDA submission there was sufficient clinical pharmacology information to support approval of the dasatinib tablet dose for the treatment of chronic phase CML in pediatric patients.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Source: Combined Clinical/Statistical Review by Drs. Ershler and Ly. For further details, please see their combined review.

The safety and efficacy of dasatinib in pediatric subjects with Ph+ CML in chronic phase is based on data from two clinical trials provided in this application (CA180018 and CA180226). Data from a third study, CA180038, was not integrated because this study used a different dosing regimen, but was provided as supportive safety data.

Trial Design

Study CA180018

Study CA180018 is a phase 1, open-label, dose-escalation (3+3 design, intra-subject dose escalation) study in which eligible subjects were treated with dasatinib orally once daily until disease progression, intolerable toxicity, or patient/physician preference.

Three strata were defined as follows:

- Stratum 1: imatinib-resistant or imatinib-intolerant Philadelphia chromosome positive (Ph+) CML in chronic phase
- Stratum 2/3:
  - Imatinib resistant or imatinib-intolerant Ph+ CML in accelerated phase, or in myeloid blast phase (MBP) or lymphoid blast phase (LBP)
  - Relapsed or refractory Ph+ ALL after imatinib
  - Second or subsequent relapse of Ph+ AML
- Stratum 4: second or subsequent relapse of Philadelphia chromosome-negative (Ph-) ALL or Ph- AML

The starting dose for each stratum was 60 mg/m^2 orally once daily. The table below provides the dose levels used for escalation of the starting dose on a per stratum-basis and for intra-subject dose escalation.

Dose Level	Dose
-1	50 mg/m^2 daily (-17%)
1	60 mg/m^2 daily (starting dose)
2	80 mg/m^2 daily (+33%)
3	100 mg/m^2 daily (+25%)
4	120 mg/m^2 daily (+20%)

Source: Clinical/Statistical Review

The primary objective of the trial was to establish, by stratum using a dose-finding design, a recommended Phase 2 dose of dasatinib in children and adolescents with relapsed or refractory leukemia.

Study CA180226

Study CA180226 was a phase 2, open-label, non-randomized, multi-center trial in pediatric patients age 0 to 18 years with newly diagnosed CML who were treatment-naive and with CP-CML, Ph+ ALL or with AP-CML or BPCML, who relapsed after, or were resistant or intolerant to imatinib. This study enrolled subjects on 3 cohorts based on underlying disease and prior treatment, as follows:

- Cohort 1: Ph+ CP-CML with resistance or intolerance to imatinib
- Cohort 2: AP/BP-CML or Ph+ ALL with resistance or intolerance to imatinib
- Cohort 3: Newly diagnosed Ph+ CP-CML

Cohort 3 was further subdivided into 2 subgroups:

- Cohort 3a: Tablet formulation
- Cohort 3b: PFOS formulation

All subjects received dasatinib orally once daily until disease progression, intolerable toxicity, or subject/physician preference. The following doses were administered:

- Cohort 1: Dasatinib 60 mg/m^2 once daily (maximum dose of 100 mg daily for subjects with high BSA)
- Cohort 3a: Dasatinib tablets 60 mg/m^2 once daily
- Cohort 3b: Dasatinib PFOS 72 mg/m^2 once daily.

Efficacy was assessed by cohort and sub-cohort for all treated subjects. The primary objectives of each cohort are listed below.

Primary Objectives:

- To estimate the major cytogenetic response (MCyR) rate to dasatinib therapy in children and adolescents with CP-CML who proved resistant to or intolerant of imatinib (Cohort 1).
  - The rate of MCyR was defined as complete (0%) or partial (1-35%) of Ph+ metaphases in at least 20 metaphases in the bone marrow.
- To estimate the complete hematologic response (CHR) rate in children and adolescents with Ph+ ALL, AP-CML and BP CML who were resistant to, intolerant to, or who relapsed after prior imatinib therapy (Cohort 2).
  - The rate of CHR including no more than 5% blasts in the bone marrow and normal WBC without blasts in the peripheral blood
- To estimate the complete cytogenetic response (CCyR) rate to dasatinib therapy in children and adolescents with newly diagnosed CP-CML who are treatment naïve (except hydroxyurea) (Cohort 3).

Trial Results

In Study CA180018, 17 pediatric patients with CP-CML that was resistant or intolerant of imatinib were enrolled in Stratum 1. In Study CA180226, 29 pediatric patients with CP-CML that was resistant or intolerant of imatinib were enrolled in Cohort 1, 84 pediatric patients with newly diagnosed CP-CML were enrolled in Cohort 3 (51 in Cohort 3a and 33 in Cohort 3b).

The table below presents the overall response rates for the pooled imatinib-resistant resistant/intolerant CP-CML patients in Studies CA180018 and CA180226 (Stratum 1 and Cohort 1) and the newly diagnosed treatment naïve CP-CML patients in Study CA180226 (Cohort 3a), all taking the tablet formulation of dasatinib. The overall MCyR, CCyR, MMR rates for the imatinib resistant/intolerant CP-CML patients were 89.1%, 82.6%, and 56.5%, respectively. The overall MCyR, CCyR, MMR rates for the newly diagnosed treatment naive CP-CML patients were 98%, 96.1%, and 88.2%, respectively.

Table 4. Results for overall Response Rate

	Imatinib-resistant or intolerant Ph+ CP-CML			Cohort 3: Newly Dx Treatment Naïve Ph+ CP-CML
	Stratum 1 60 and 80 mg/m2 tablet (N=17)	Cohort 1 60 mg/m2 tablet (N=29)	Total (N=46)	Cohort 3A 60 mg/m2 Tablet (N=51)
MCyR Overall	15 (88.2% (64%, 98%)) *	26 (89.8% (72.6%, 97.8%))	41 (89.1% (76.4%, 96.3%))	50 (98% (89.6%, 99.9%))
CCyR Overall	14 (82.4% (57%, 96.2%))	24 (82.8% (64.2%, 94.2%))	38 (82.6% (68.6%, 92.2%))	49 (96.1% (86.5%, 99.5%))
MMR Overall	8 (47.1% (23%, 72.1%))	18 (62.1% (42.2%, 79.3%))	26 (56.5% (41.1%, 71.1%))	45 (88.2% (76.1%, 95.6%))

*Count (Response Rate (95% Confidence Interval))

Source: Clinical/Statistical Review

8. Safety

Source: Combined Clinical/Statistical Review by Drs. Ershler and Ly. For further details, please see their combined review.

Assessment of the safety of dasatinib in pediatric patients with chronic phase CML is based on the findings from studies CA180018 and CA180226, with support from study CA180038. A total of 130 pediatric subjects with Ph+ CP-CML were treated with dasatinib once daily dosing in studies CA180018 and CA180226 and make up the pooled safety population. Of these, 84 subjects were treatment-naïve and 46 were previously treated and were refractory to or intolerant of imatinib.

Overall, the safety profile of dasatinib in pediatric patients is similar to that in adults. There were no unexpected safety findings.

- There were four deaths in the pooled patient population, all of which occurred in subjects who were previously treated and resistant or intolerant to imatinib. There were no deaths in the treatment naïve patient population. The four deaths all occurred after treatment completion and there were no deaths during treatment or within 30 days of the last treatment dose of dasatinib. One subject died due to disease progression. The other deaths were due to fatal bleeding, respiratory failure, and digestive tract bleeding.

- In the pooled patient population, SAEs were reported in 37.7% of subjects. A total of 21 subjects (45.7%) in the imatinib resistant/intolerant treatment group, and 28 (33.3%) in the treatment naïve group experienced at least one serious adverse event (SAE). The most common SAEs overall were anemia, pyrexia and gastroenteritis.

- In the pooled patient population, almost all patients (99.2%) experienced at least one TEAE, and 84 (64.4%) experienced at least 1 Grade 3 or 4 TEAE. The most common TEAEs in all treatment groups were abdominal pain (63%), diarrhea (53%), headache (53%), vomiting (45%) and pyrexia (43%). Grade 3-4 AEs were reported in 84 subjects

(64.6%) in the pooled patient population. The most frequent Grade 3-4 AEs were neutropenia (28.5%) and thrombocytopenia (14.6%).

- Identified adverse events of special interest identified for dasatinib include fluid retention, pulmonary arterial hypertension, hemorrhage, cardiac events, and fatigue.
    - Overall, in the pooled patient population, 34 subjects (26.2%) experienced superficial edema and 4 (3.1%) experienced generalized edema. Most of these events were mild in severity with only one subject experiencing a Grade ≥3 event (Grade 3 periorbital edema).
    - One subject, an 11 year old male with newly diagnosed CP-CML, experienced Grade 1 pulmonary arterial hypertension 1016 days after starting treatment with dasatinib.
    - Treatment-emergent bleeding events occurred in 35 (26.9%) of subjects. Most of these were mild in severity. Two subjects experienced Grade ≥ 3 gastrointestinal bleeding.
    - The incidence of cardiac disorders was 4.6%, no grade ≥ 3 events occurred.
    - The incidence of fatigue was 37%.

9. Advisory Committee Meeting

This efficacy supplement was not presented to the Oncologic Drugs Advisory Committee because the application did not raise significant efficacy or safety issues for the proposed indication.

10. Pediatrics

This is a supplemental application for dasatinib for pediatric patients with Ph+ CML in chronic phase. A pediatric Written Request (WR) was issued on 9/17/2007, followed by four amendments (10/13/2002, 7/23/2103, 5/29/2014, 3/4/2015). The WR described the development of dasatinib in pediatric patients with imatinib-resistant chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia (CP, AP, and BP CML), as well as development in pediatric ALL. (b) (4) This supplement represents a partial fulfillment of the WR.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP):** No Issues
- **Financial disclosures:** In accordance with 21 CFR 54, the Applicant submitted the required financial disclosure requirement and certification for Studies CA180018, CA180038, and CA180226. No investigators or sub-investigators declared financial interests.
- **Other GCP issues:** None.
- **OSI audits:** OSI audits were performed for Study CA180226 at two clinical sites (Drs. Gore and Cardos). The study data derived from these clinical sites was considered to be

reliable in support of the requested indication. The final regulatory classification for inspection of Dr. Gore is No Action Indicated (NAI). The preliminary regulatory classification for inspection of Dr. Cardos is Voluntary Action Indicated (VAI).

There were no other outstanding regulatory issues.

12. Labeling

The Prescribing Information is currently under negotiation. DMEPA, OPDP, DMPP and the Division's Associate Director for Labeling participated in labeling discussions and provided recommendations.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Approval

- Risk Benefit Assessment

  The efficacy and safety results of Studies CA180018 and CA180226 demonstrate an acceptable benefit-risk profile for dasatinib for the treatment of pediatric patients with Philadelphia chromosome positive (Ph+) Chronic Phase Chronic Myeloid Leukemia (CP-CML).

  The proposed dosing regimen for this indication was 60 mg/m^2 once daily, with weight-tiered dosing proposed for the formulation.

  All review team members recommended approval.

  The efficacy of dasatinib in pediatric patients with CP-CML is based on the results of the phase 1 study CA180018 and the pivotal Phase 2 study CA180226. Findings from these studies demonstrate that dasatinib results in clinically significant responses in pediatric patients with Ph+ CML in chronic phase, including those who are treatment-naïve, as well as those who were previously resistant to or intolerant of imatinib.

  The overall response rates exceeded the clinically relevant thresholds specified in these studies. The cumulative MCyR, CCyR and MMR rates at 24 months for the imatinib resistant/intolerant CP-CML patients were 89.1%, 82.6%, and 56.5%, respectively. The cumulative MCyR, CCyR and MMR rates at 24 months for the newly diagnosed treatment naive CP-CML patients were 98%, 96.1%, and 88.2%, respectively.

  Additionally, the efficacy results showed increasing trends for cumulative response rates for CCyR, MCyR and MRR over time, from 3 months to 24 months. The

overall efficacy findings support the proposed indication for dasatinib in pediatric subjects with Ph+ CML in chronic phase.

The safety profile of dasatinib is acceptable for the proposed patient population. The most common treatment-emergent adverse evets were abdominal pain, diarrhea, headache, vomiting and pyrexia. There were no cases of pleural or pericardial effusion related to dasatinib observed in the studies of pediatric subjects with CP-CML.

No new safety signals were identified in the review.

Based on the above, I recommend regular approval for dasatinib for the treatment of pediatric patients with Philadelphia chromosome positive (Ph+) Chronic Phase Chronic Myeloid Leukemia (CP-CML).

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

  No risk management measures are recommended to support the approval of this efficacy supplement.

- Recommendation for other Postmarketing Requirements and Commitments

  No new postmarketing requirements or commitments are recommended to support the approval action for this application.

- Recommended Comments to Applicant: None

References:

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/s/

NICOLE J GORMLEY
11/09/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21986Orig1s020

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	021986, S-020
Priority or Standard	Priority
Submit Date(s)	May 9, 2017
Received Date(s)	May 9, 2017
PDUFA Goal Date	November 9, 2017
Division / Office	Division of Hematology Products/Office of Hematology and Oncology Products
Reviewer Name(s)	Rachel Ershler, MD (Clinical Reviewer) Thomas Ly, PhD (Statistical Reviewer)
Review Completion Date	October 6, 2017
Established Name	Dasatinib
(Proposed) Trade Name	Sprycel®
Therapeutic Class	Tyrosine Kinase Inhibitor
Applicant	Bristol-Myers Squibb Company
Formulation(s)	Oral tablets
Dosing Regimen	Weight based dosing: 10 to < 20 kg: 40 mg 20 to < 30 kg: 60 mg 30 to < 45 kg: 70 mg At least 45 kg: 100 mg
Indication(s)	For the treatment of pediatric patients with Philadelphia Chromosome Positive (Ph+) Chronic Myelogenous Leukemia (CML) in Chronic Phase.

Template Version: March 6, 2009

Table of Contents

Table of Tables

Table 1. List of Abbreviations

ADR	Adverse drug reaction
AE	Adverse event
ALC	Absolute lymphocyte count
ALL	Acute lymphoblastic leukemia
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AP	Accelerated phase
AR	Adverse reaction
AST	Aspartate aminotransferase
BID	Twice per day
BM	Bone marrow
BMI	Body mass index
BP	Blast phase
BSA	Body surface area
BUN	Blood urea nitrogen
CBC	Complete Blood Count
CCyR	Complete cytogenetic response
CHR	Complete hematologic response
CMC	Chemistry, manufacturing and controls
CML	Chronic myeloid leukemia
CP	Chronic phase
CR	Complete response
CrCl	Creatinine Clearance
CRF	Case report form
CSF	Cerebrospinal fluid
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
eCTD	Electronic Common Technical Document
FDA	Food and Drug Administration
HBV	Hepatitis B virus
HSCT	Hematopoietic stem cell transplantation
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IND	Investigational New Drug
IRB	Institutional Review Board
IRC	Independent Review Committee

ISE	Integrated summary of efficacy
ISS	Integrated summary of safety
ITT	Intention-to-treat
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MCyR	Major cytogenetic response
NDA	New Drug Application
PB	Peripheral blood
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PFOS	Powder for oral suspension
Ph+	Philadelphia chromosome
PK	Pharmacokinetics
PLT	Platelet Count
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	Standard of care
TEAE	Treatment emergent adverse event
ULN	Upper limit of normal
WBC	White Blood Cell Count

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This clinical reviewer recommends regular approval of the efficacy supplement sNDA 021986, S-020 for dasatinib for the treatment of pediatric patients with Philadelphia Chromosome Positive (Ph+) Chronic Myelogenous Leukemia (CML) in Chronic Phase (CP). This recommendation is based on the safety and efficacy findings of Study CA180018 entitled, "Phase 1 study of SRC/ABL tyrosine kinase inhibitor dasatinib (BMS-354825) in children and adolescents with relapsed or refractory leukemia", and the safety and efficacy findings of Study CA180226 entitled, "A phase 2 study of dasatinib therapy in children and adolescents with newly diagnosed chronic phase chronic myelogenous leukemia or with Ph+ leukemias resistant or intolerant to imatinib".

1.2 Risk Benefit Assessment

Background
CML is relatively rare among children and adolescents and constitutes 2% of all leukemias in children younger than 15 years and 9% of all leukemias in adolescents between 15 and 19 years, with an annual incidence of 1 and 2.2 cases per million in these two age groups, respectively.[1] In general, while CML in children arises from the same gene fusion as adults (*BCR*-ABL1), pediatric CML tends to have a more aggressive clinical course than adult CML and patients tend to present with more significant clinical findings, such as larger spleen sizes and higher baseline WBC counts.

The therapeutic approach to CML changed with the introduction of the tyrosine kinase inhibitors (TKIs) of the BCR-ABL fusion oncoprotein. Imatinib, an oral TKI was approved for use in adults in 2001 and was first approved for use in pediatric patients with CP-CML who received bone marrow transplant or in patients resistant to interferon alpha therapy in 2003. Use of imatinib in pediatric chronic phase CML was expanded in the US in September 2006. Imatinib has since become the standard first-line therapy and the only TKI therapy approved to treat pediatric Ph+ CP-CML. Despite the effectiveness of imatinib, approximately 10% to 30% of all adult and pediatric patients discontinue from imatinib due to intolerance of adverse drug effects, or to declining response to treatment or progression of disease due, in part, to the presence or development of imatinib-resistant BCR-ABL mutations.[3]

Dasatinib is a second generation tyrosine kinase inhibitor that was first approved for use in 2006 under the accelerated approval regulations for the treatment of adults with chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy, as well as for the treatment of adults with Ph+ ALL with resistance or intolerance to prior therapy. In October 2010, dasatinib was approved for the treatment of adults with newly diagnosed Ph+ CML in chronic phase.

The dasatinib clinical pediatric development program was initiated in 2006 in the US under IND 66,971 and in 2009 in the EU, and spans across CML, AML, and ALL.

A pediatric Written Request (WR) was issued on 9/17/2007, followed by four amendments (10/13/2002, 7/23/2103, 5/29/2014, 3/4/2015). The WR described the development of dasatinib in pediatric patients with imatinib-resistant chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia (CP, AP, and BP CML), as well as development in pediatric ALL. (b) (4)

(b) (4)

This is a supplemental application for dasatinib for pediatric patients with Ph+ CML in chronic phase.

Efficacy
The efficacy of dasatinib in pediatric patients with CP-CML is based on the results of the phase 1 study CA180018 and the pivotal Phase 2 study CA180226. Findings from these studies demonstrate that dasatinib use results in clinically significant responses in pediatric patients with Ph+ CML in chronic phase, including those who are treatment-naïve, as well as those who were previously resistant to or intolerant of imatinib.

The overall response rates exceeded the clinically relevant thresholds specified in these studies. The cumulative MCyR, CCyR and MMR rates at 24 months for the imatinib resistant/intolerant CP-CML patients were 89.1%, 82.6%, and 56.5%, respectively. The cumulative MCyR, CCyR and MMR rates at 24 months for the newly diagnosed treatment naive CP-CML patients were 98%, 96.1%, and 88.2%, respectively. Additionally, the efficacy results showed increasing trends for cumulative response rates for CCyR, MCyR and MRR over time, from 3 months to 24 months.

The overall efficacy findings support the proposed indication for dasatinib in pediatric subjects with Ph+ CML in chronic phase.

Safety
Assessment of the safety of dasatinib in pediatric patients with chronic phase CML is based on the findings from studies CA180018 and CA180226, with support from study CA180038. A total of 130 pediatric subjects with Ph+ CP-CML were treated with dasatinib once daily dosing in studies CA180018 and CA180226 and make up the pooled safety population. Of these, 84 subjects were treatment-naïve and 46 were previously treated and were refractory to or intolerant of imatinib.

Overall, the safety profile of dasatinib in pediatric patients is similar to, or better than, that in adults. There were no unexpected safety findings. The most common treatment-emergent adverse evets were abdominal pain, diarrhea, headache, vomiting and pyrexia. There were no cases of pleural/pericardial effusion, pulmonary

edema/hypertension, or arterial pulmonary hypertension related to dasatinib observed in the studies of pediatric subjects with CP-CML.

There were four deaths in the pooled patient population, all of which occurred in subjects who were previously treated and resistant or intolerant to imatinib. There were no deaths in the treatment naïve patient population. The four deaths all occurred after treatment completion and there were no deaths during treatment or within 30 days of the last treatment dose of dasatinib.

Overall Benefit-Risk Assessment for the Proposed Indication

The risk-benefit assessment supports regular approval for the proposed indication.

Table 2. Risk Benefit Assessment

Decision Factor	Evidence and Uncertainties	Conclusions
Analysis of Condition	CML constitutes 2% of all leukemias in children younger than 15 years and 9% of all leukemias in adolescents between 15 and 19 years, with an annual incidence of 1 and 2.2 cases per million in these two age groups, respectively.[1]	CML is a serious and life-threatening condition.
Unmet Medical Need	Currently, no consensus guidelines exist for the treatment of pediatric CML. However, the therapeutic approach to CML changed with the introduction of tyrosine kinase inhibitors (TKIs). Imatinib has become the standard first-line therapy and the only TKI therapy approved for use in pediatric subjects with CP-CML. Approximately 10-30% of pediatric patients discontinue imatinib due to intolerance, declining response or progressive disease. There is no TKI approved for use in pediatric subjects who are intolerant to or resistant to imatinib.	Additional therapeutic options are needed for children with Ph+ CML.
Clinical Benefit	The clinical benefit of dasatinib in pediatric patients with Ph+ CP-CML was determined by the efficacy results of studies CA180018 and CA180226. • For treatment-naïve subjects, cumulative response at 24 months: - MCyR: 98% - CCyR: 96.1% - MMR: 88.2% - Median durations of MCyR, CCyR, MMR: not reached • For Imatinib resistant/intolerant subjects, cumulative response at 24 months: - MCyR: 89.1% - CCyR: 82.6% - MMR: 56.5%	Dasatinib use in pediatric subjects with CP-CML (both treatment-naïve and imatinib resistant/intolerant) resulted in high overall response rates, including MCyR, CCyR and MMR, as well as increasing trends in cumulative response rates over time.

	- Median durations of MCyR, CCyR, MMR: not reached	
Risks	The safety population used to support this application included 130 pediatric subjects with CP-CML who received once daily dosing with dasatinib. • The median duration of exposure to dasatinib was 42.3 months • Serious adverse reactions) were reported in 49 (37.7%) of subjects. • The most frequent adverse reactions were abdominal pain, diarrhea, vomiting, headache, pyrexia. • There were four deaths in the pediatric patient population, all in patients who were refractory to/intolerant of imatinib. No deaths occurred while receiving dasatinib therapy or within 30 days after stopping therapy. • Adverse events of special interest were examined because of their association with dasatinib in the currently approved indications. - The incidence of fluid retention was similar to that in adults - There were no events of pericardial effusion or pulmonary edema. - Other AEs of special interest were less frequent than seen in the adult data.	Overall, the safety profile of dasatinib in pediatric subjects with Ph+ CML in chronic phase appears to be similar to, if not better than that observed in adults.
Risk Management	Prescribers should be aware of the risks associated with dasatinib use including myelosuppression, bleeding events, fluid retention, cardiac dysfunction, pulmonary arterial hypertension, severe dermatologic reactions, QT prolongation, tumor lysis syndrome, embryo-fetal toxicity, and effects on growth and development in pediatric patients. The proposed labeling includes warnings and precautions including recommended monitoring, and dose modifications. Safe use will require that both patients and healthcare providers are aware of these instructions.	Based on the findings in pediatric subjects, it is recommended that the label continue to contain warnings for myelosuppression, bleeding events, fluid retention, cardiac dysfunction, and pulmonary arterial hypertension. An additional warning will be added regarding the effects on growth and development in pediatric patients with directions to monitor bone growth and development in pediatric patients.

Source: FDA Clinical Reviewer

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

No post-marketing commitments (PMCs) or post-marketing requirements (PMRs) are necessary for this supplement.

2 Introduction and Regulatory Background

Chronic Myeloid Leukemia
Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm that accounts for approximately 15-20% of leukemias in adults. It has an annual incidence of 1-2 cases/100,000 with a slight male predominance. CML is associated with the fusion of two genes: BCR on chromosome 22 and ABL1 on chromosome 9, resulting in the BCR-ABL1 fusion gene. This abnormal fusion results from a reciprocal translocation between chromosomes 9 and 12, t(9;22)(q34;q11) that produces an abnormal chromosome, Philadelphia (Ph) chromosome.

CML typically has a triphasic clinical course that includes the following:

- Chronic Phase (CP):
  - <10% blasts in PB or BM
  - Approximately 90% of CML at diagnosis is in chronic phase
  - Without treatment, CML in chronic phase will eventually progress to accelerated phase and blast phase.
- Accelerated Phase (AP): Recent revisions to the WHO criteria (2016) define this phase by any 1 or more of the following:
  - Persistent or increasing WBC (>10 x 10^9/L), unresponsive to therapy
  - Persistent or increasing splenomegaly, unresponsive to therapy
  - Persistent thrombocytosis (>1000 x 10^9/L), unresponsive to therapy
  - Persistent thrombocytopenia (<100 x 10^9/L) unrelated to therapy
  - ≥20% basophils in the PB
  - 10-19% blasts in the PB or BM
  - Additional clonal chromosomal abnormalities in Ph+ cells at diagnosis
  - Any new clonal chromosomal abnormality in Ph+ cells that occurs during therapy
  - “Provisional” response to TKI:
    - Hematologic resistance to the first TKI (or failure to achieve a complete hematologic response to the first TKI)
    - Any hematological, cytogenetic, or molecular indications of resistance to 2 sequential TKIs
    - Occurrence of 2 or more mutations in *BCR-ABL1* during TKI therapy.
- Blast Phase (BP): Defined by one or more of the following:
  - ≥20% peripheral blood or bone marrow blasts

- Large foci or clusters of blasts on the bone marrow biopsy
- Presence of extramedullary blastic infiltrates

Clinical Manifestations
Clinical findings at the time of diagnosis depend on the phase of the disease. Approximately 20-50% of patients are asymptomatic and CML is diagnosed based on incidental laboratory findings. Among symptomatic patients, the most common symptoms are fatigue (34%), abnormal bleeding (21%), weight loss (20%) and excessive sweating (15%). Frequent findings include splenomegaly (48-76%), anemia (45-62%), elevated white blood cell count above 100,000/μL (52-72%) and elevated platelet count (15-34%). Patients in blast crisis may also have extramedullary involvement such as the lymph nodes, skin and soft tissues.

Chronic Myeloid Leukemia in Pediatrics
CML is relatively rare among children and adolescents and constitutes 2% of all leukemias in children younger than 15 years and 9% of all leukemias in adolescents between 15 and 19 years, with an annual incidence of 1 and 2.2 cases per million in these two age groups, respectively.[1] In general, while CML in children arises from the same gene fusion as adults (*BCR*-ABL1), pediatric CML tends to have a more aggressive clinical course than adult CML and patients tend to present with more significant clinical findings, such as larger spleen sizes and higher baseline WBC counts. The proportion of pediatric patients diagnosed with advanced-stage disease (accelerated phase or blast phase) is higher than for adults.[2]

Standard Treatment for Ph+ Chronic Phase CML
Prior to 2006, the standard treatment for pediatric subjects with Ph+ CML in chronic phase included a combination of chemotherapy, hematopoietic stem cell transplant (HSCT) and/or enrollment on clinical trials. The therapeutic approach to CML changed with the introduction of TKIs of the BCR-ABL fusion oncoprotein, starting with imatinib in 2001. Imatinib was first approved for use in pediatric CP-CML in patients who received bone marrow transplant after stem cell transplantation or in patients resistant to interferon alpha therapy (US: May 2003, EU: December 2002). Use of imatinib in pediatric chronic phase CML was expanded in the US on September 27, 2006 and in the EU on September 13, 2006, based on data from a phase II clinical study in newly-diagnosed CML.

Imatinib has since become the standard first-line therapy and the only TKI therapy approved to treat pediatric Ph+ CP-CML. Despite the effectiveness of imatinib, approximately 10% to 30% of all adult and pediatric patients discontinue from imatinib due to intolerance of adverse drug effects, or to declining response to treatment or progression of disease due, in part, to the presence or development of imatinib-resistant BCR-ABL mutations.[3]

Reviewer Comment: CML in pediatric patients is a serious and life-threatening disease and new treatments are needed.

2.1 Product Information

Established Name: Dasatinib

Trade Name: Sprycel®

Drug Class: Tyrosine kinase inhibitor (second generation)

Indications: Dasatinib is currently approved in the US for the following indications:
- Newly diagnosed adults with Philadelphia chromosome-positive (Ph+) CML in chronic phase.
- Adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib.
- Adults with Ph+ ALL with resistance or intolerance to prior therapy.

Proposed Indication: For the treatment of pediatric patients with Ph+ CML in chronic phase.

Proposed Dosage and Administration: The dosing regimen for Sprycel® for pediatric patients is provided in the table below.

Dosage forms and strengths:
Tablets: 20 mg, 50 mg, 70 mg, 80 mg, 100 mg, 140 mg

Table 3. Dosage of Dasatinib for Pediatric Patients

Body Weight (kg)	Daily Dose (mg)
10 to less than 20 kg	40 mg
20 to less than 30 kg	60 mg
30 to less than 45 kg	70 mg
At least 45 kg	100 mg

Clinical Reviewer Comment: The Applicant (b) (4) (b) (4). (b) (4) (b) (4).

2.2 Tables of Currently Available Treatments for Proposed Indications

Treatment of CML is based on the disease phase. Available treatments for pediatric CML in chronic phase are provided in the table below.

Table 4. Approved Treatments for Pediatric CML

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues
Imatinib (Gleevec®)	Newly diagnosed adult and pediatric patients with Ph+ CML in chronic phase	2001: Initial imatinib approval 2011: Approved for pediatric use	340 mg/m^2/day Orally	Results from pivotal Phase 2 study: - CHR at 8 weeks: 78% - CCyR: 65%	- Edema/fluid retention - Cytpenias - CHF/LV dysfunction - Hepatotoxicity - Grade 3/4 hemorrhage - Gastrointestinal perforations - Bullous dermatologic reactions - Renal toxicity - Tumor lysis syndrome

Source: FDA Clinical Reviewer

2.3 Availability of Proposed Active Ingredient in the United States

Sprycel® is currently marketed in the United States as a tablet for oral administration.

2.4 Important Safety Issues With Consideration to Related Drugs

Commercially available tyrosine kinase inhibitors include Sprycel® (dasatinib), Gleevec® (imatinib), Tasigna® (nilotinib), Tarceva® (erlotinib), Bosulif® (bosutinib), and Iclusig® (ponatinib). The most common overlapping toxicities include myelosuppression, fluid retention/edema, hepatic toxicity and embryo-fetal toxicity. The table below summarizes the main toxicities listed in the Warnings and Precautions section of each label.

Table 5. Kinase Inhibitors: Warnings and Precautions

	Dasatinib	Imatinib	Nilotinib	Erlotinib	Bosutinib	Ponatinib
Myelosuppression	X	X	X		X	X
Hemorrhage in patients taking warfarin				X		
Bleeding related events	X	X				X
Microangiopathic hemolytic anemia with thrombocytopenia				X		
Fluid retention/edema	X	X			X	X
Sudden deaths (ventricular repolarization abnormality)			X			
Arterial Occlusion						X*

Venous thromboembolism						X*
Cardiac dysfunction	X					
QT prolongation	X		X			
Cardiac arrhythmias						X
Congestive heart failure, LV dysfunction		X				X*
Cerebrovascular accident				X		
Cardiac and vascular events		X				
Hypertension						X
Neuropathy						X
Pancreatitis and elevated serum lipase			X			X
Pulmonary arterial hypertension	X					
Interstitial lung disease				X		
Embryo-fetal toxicity	X	X	X	X	X	X
Hepatotoxicity		X	X	X	X	X*
Renal failure				X		
Ocular disorder						X
Reversible posterior leukoencephalopathy syndrome (RPLS)						X
Hypothyroidism		X				
Tumor lysis syndrome	X					X
Gastrointestinal perforations		X	X			X
Growth Retardation		X				
Gastrointestinal toxicity					X	
Electrolyte abnormalities			X			
Toxicities from long-term use		X				
Dermatologic toxicities	X	X	X			
Compromised wound healing						X
Driving and using machinery		X				
Drug interactions and Food effects			X			

* Boxed warning
Source: FDA Clinical Reviewer

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Dasatinib was first approved in the US on June 28, 2006 under the accelerated approval regulations for the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib and on the same day (June 28, 2006) received regular approval for the treatment of adults with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) with resistance or intolerance to prior therapy. Safety and efficacy were supported by four single-arm multicenter trials which enrolled a combined 445 patients with chronic phase (CP) chronic myeloid leukemia (CML), accelerated phase (AP) CML, or myeloid or lymphoid blast phase (BP) CML and Ph+ ALL. In patients with CP-CML, the major cytogenetic response (MCyR) rate was 45%, with a complete cytogenetic response (CCyR) rate of 33%. Median response durations had not been reached. The approved dosing schedule was 70 mg twice daily (BID). However, this dose schedule was found to be associated with frequent dose interruptions and reductions due to considerable myelosuppression and fluid retention (especially pleural effusion) resulting in a median actual average daily dose close to 100 mg per day in prior clinical trials.

On November 8, 2007, dasatinib received accelerated approval for the new dosing regimen of 100 mg once daily (QD) for the treatment of patients with chronic phase Ph+ CML with resistance or intolerance to imatinib due to insufficient long-term efficacy and safety data (S-001, S-002). The 100 mg QD dosing schedule was based on one dose-optimizing trial (CA180034) in which patients randomized to 100 mg QD had comparable rates of MCyR and less toxicity than those receiving 70 mg BID.

On May 21, 2009, FDA converted the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase CML with resistance or intolerance to prior therapy including imatinib to regular approval. With this conversion, the new dosing regimen of 100 mg QD also received regular approval based on the 24 month follow-up data of the CA180034 trial.

On October 10, 2010, dasatinib was approved for the treatment of adults with newly diagnosed Ph+ CML in chronic phase.

Pediatric Regulatory History
The dasatinib clinical pediatric development program was initiated in 2006 in the US under IND 66,971 and in 2009 in the EU, and spans across CML, AML, and ALL.

A pediatric Written Request (WR) was issued on 9/17/2007, followed by four amendments (10/13/2002, 7/23/2103, 5/29/2014, 3/4/2015). The WR described the development of dasatinib in pediatric patients with imatinib-resistant chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia (CP, AP, and

BP CML), as well as development in pediatric ALL. (b) (4)

(b) (4)

Global pediatric development has been ongoing since 2009, and is in accordance with both the FDA agreed-upon WR and the European Pediatric Investigational Plan (PIP) for CML and Ph+ ALL (EMEA-000567-PIP01-09-M04).

(b) (4)

The data submitted in this application package is a partial response to the WR.

2.6 Other Relevant Background Information

Dasatinib received orphan drug designation on November 28, 2005 for the treatment of chronic myelogenous leukemia under the provisions of section 526 of the Federal, Food, Drug and Cosmetic Act. As a result, dasatinib is exempt from the Pediatric Research Equity Act (PREA) requirement.

(b) (4)

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This supplement was submitted as an electronic Common Technical Document (eCTD) and follows the FDA Guidance for Industry: Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications. The overall quality and integrity of this sNDA were adequate to allow review.

3.2 Compliance with Good Clinical Practices

The clinical trials used to support this application, CA180018, CA180038 and CA180226, were conducted in accordance with Good Clinical Practice as defined by the International Conference on Harmonization and in accordance with the ethical principles underlying European Union Directive 2001/20/EC.

3.3 Financial Disclosures

The applicant submitted financial disclosure information, including relevant Forms 3454, for the Bristol-Myers Squibb (BMS) sponsored trials, CA180018 and CA180226, as well as the National Cancer Institute (NCI)/Cancer Therapy Evaluation Program (CTEP) Sponsored trial CA180038.

Study CA180018
Financial disclosure information was collected for 85 Investigators (Primary Investigators and Sub-investigators) participating in this study. Of these, 83 investigators/sub-investigators had information available and reported. No investigator or sub-investigator had financial disclosable information. No financial disclosure information is available for two of the sub-investigators because both of them left the site before Financial Disclosure was completed and no further information was obtained.

Study CA180038
CA180038 was sponsored by the National Cancer Institute (NCI)/Cancer Therapy Evaluation Program (CTEP). As part of CTEP operating procedures financial disclosure information is updated annually using a standard form that contains 4 questions regarding financial interests. The 4 responses are entered into an enterprise database. BMS provided the list of investigators who participated in the CA180038 study to CTEP. CTEP queried all 26 investigators who participated as Medical Doctors in CA180038 for possible conflict of interest with Bristol-Myers Squibb. All 26 of the principal investigators had no financial information to disclose.

Study CA180226
Financial disclosure information was collected and reported for 528 Investigators (Primary investigators and Sub-investigators) participating in this study. Of these, 525 had information available and reported. No investigator or sub-investigator had financial disclosable information. No financial disclosure information is available for 3 of the investigators because both of them left the site before Financial Disclosure was completed and no further information was obtained.

No investigators or sub-investigators in any of the clinical studies used to support this application were BMS employees.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new CMC information was submitted in this sNDA. There is no change in product manufacturing for this supplement.

(b) (4)

4.2 Clinical Microbiology

Refer to the CMC Review.

4.3 Preclinical Pharmacology/Toxicology

No new pharmacology/toxicology information was submitted in this sNDA and there are no proposed changes for the pharmacology/toxicology-related sections of the label.

The pediatric age ranges supported by toxicology studies for dasatinib in rats include birth through 2 years old (peri- and postnatal development study) and prepubescent children through adulthood (repeat-dose toxicology studies). The pediatric age ranges supported by monkey toxicology studies support children of 6 years old through adulthood (repeat-dose toxicology studies). Based on the age-range of animals used in this comprehensive battery of nonclinical toxicity studies in both rats and monkeys, these studies will support the pediatric use of dasatinib from birth to adulthood. The available nonclinical toxicology and clinical data for dasatinib indicate that humans (adults or children) are less sensitive to the toxicity of dasatinib than rats or monkeys. Further, the adult human experience adequately predicted the pediatric safety profile for dasatinib. Notably, there are no novel toxicities that have been observed in children, nor have toxicities in children been reported at lower therapeutic exposures. These data collectively indicate a favorable risk-benefit profile for dasatinib in children with CML. For these reasons, no additional nonclinical toxicology studies were conducted with dasatinib to support the pediatric indications, which is consistent with the ICH S9 guidance that states that a dedicated nonclinical toxicology study in juvenile animals is not needed to support a pediatric registration of anticancer drugs.

4.4 Clinical Pharmacology

The clinical pharmacology profile of dasatinib in the pediatric cancer patients has been characterized based on the results of 7 clinical studies (CA180018, CA183038, CA180226, (b) (4)

The following aspects of clinical pharmacology were not studied in pediatric subjects: the assessment of dasatinib ADME, the effect of disease state, race, gender and hepatic impairment, food effect, and drug-drug interactions. These aspects have been studied previously in adult subjects, and the findings are expected to also apply to the pediatric population, based on the similar PK characteristics of dasatinib in these two populations

4.4.1 Mechanism of Action

Dasatinib is a potent broad-spectrum, competitive inhibitor of multiple oncogenic tyrosine kinases and kinase families, including BCR-ABL, SRC, c-KIT, platelet-derived growth factor receptor (PDGFR), and ephrin receptor kinases. Dasatinib is ~325-fold more potent than imatinib in inhibiting BCR-ABL in vitro.

4.4.2 Pharmacodynamics

Refer to the Clinical Pharmacology Review for further details.

4.4.3 Pharmacokinetics

The PK of dasatinib in pediatric cancer was characterized by a non-compartmental analysis (NCA) using data from the two Phase 1 studies, CA180018 and CA180038, as well as by the population pharmacokinetic (PPK) analysis using data from these Phase 1 studies pooled with data from a the Phase 2 study, CA180226 in pediatric patients with CML. Dose-response (D-R) and exposure-response (E-R) relationships were characterized in pediatric patients with newly diagnosed Ph+ CP-CML from the Phase 2 study CA180226.

Refer to the Clinical Pharmacology Review for additional details.

5 Sources of Clinical Data

The safety and efficacy of dasatinib in pediatric subjects with Ph+ CML in chronic phase is based on data from two clinical trials provided in this application (CA180018 and CA180226). Data from a third study, CA180038, was not integrated because this study used a different dosing regimen (BID dosing), but was provided as supportive safety data.

An overview of the clinical trials reviewed is provided in the tables below.

5.1 Tables of Studies/Clinical Trials

Table 6. Clinical Trials Reviewed

Trial Identifier (Identifier of Study Report) Trial Design	Trial Objective(s)/ Endpoint(s)	Patient Population	Treatment Details (Test Product(s); Dosage Regimen; Route)	Total No. of Subjects with CP-CML	Status
CA180018 Phase 1, non-comparative, open-label, dose-escalation Safety Efficacy PK	Establish recommended phase 2 dose (RP2D)	Pediatric patients (Age ≥1 to <21 yrs.) with R/R Leukemias (n=58) **Stratum 1: Imatinib-resistant or intolerant Ph+ CP CML (n=17)** Stratum 2/3: Imatinib resistant or intolerant advanced Ph+ leukemias (n=17) Stratum 4: Ph- AML and Ph- ALL (n=24)	Starting Dose: 60/80 mg/m^2 PO daily for 21 days Dose escalation up to 120 mg/m^2 PO daily	**17**	Ongoing
CA180226 Phase 2, open-label, non-randomized, single-arm Safety Efficacy PK	Cohort 1: MCyR (target 30%) Cohort 2: CHR Cohort 3: CCyR (target 55%)	Pediatric patients (Age 0 to 18 years) with newly diagnosed Ph+ CP CML or with Ph+ leukemias resistant or intolerant to imatinib **Cohort 1: Ph+ CP CML resistant/intolerant to imatinib (n=29)** Cohort 2: AP/BP CML or Ph+ ALL resistant or intolerant to imatinib (n=17) **Cohort 3: Newly diagnosed Ph+ CP CML (n=84)**	**Cohort 1: 60 mg/m^2 PO daily** Cohort 2: 80 mg/m^2 PO daily **Cohort 3a: 60 mg/m^2 PO daily (Tablet formulation)** **Cohort 3b: 72 mg/m^2 PO daily (PFOS formulation)**	**113** Resistant/ intolerant to imatinib: 29 Newly diagnosed: 84	Ongoing

Source: FDA Clinical Reviewer

Table 7. Supportive Clinical Study

Trial Identifier (Identifier of Study Report) Trial Design	Trial Objective(s)/ Endpoint(s)	Patient Population	Treatment Details (Test Product(s); Dosage Regimen; Route)	Total No. of Subjects with CP-CML	Status
CA180038 (COG ADVL0516) Phase 1, open-label, dose-escalation Safety, dose- finding Efficacy PK	Dose escalation PK Safety	Pediatric patients (Age ≥1 to <21 yrs.) with R/R solid tumors or imatinib-resistant Ph+ leukemias (n=38) **Stratum 2: Imatinib-resistant or intolerant Ph+ leukemias (n=11)** - **Ph+ CP-CML (n=9)** - Ph+ ALL (n=2)	Dose levels: 50 mg/m^2 PO BID 65 mg/m^2 PO BID 85 mg/m^2 PO BID	**9**	Complete

Source: FDA Clinical Reviewer

5.2 Review Strategy

The clinical review was primarily based on the following:

- Updated efficacy and safety data from studies CA180018, CA180038 and CA180226, which includes the electronic submission, clinical study reports, summary of clinical efficacy, summary of clinical safety, datasets, case report forms, etc.
- Updated relevant efficacy and safety data were reproduced
- Relevant prior regulatory history of dasatinib
- Existing product labels
- Applicant presentation to the FDA
- Relevant applicant submissions in response to the review team's information requests

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study CA180018

Study Title: Phase 1 study of SRC/ABL tyrosine kinase inhibitor dasatinib (BMS-354825) in children and adolescents with relapsed or refractory leukemia.

Study Period: March 21, 2006 (first subject first visit) – May 25, 2011 (last subject last observation)

Clinical Sites: This study was conducted at 16 sites in 7 countries. A total of 13 sites in 6 countries enrolled subjects: Austria, France, Germany, Italy, Netherlands, United Kingdom.

Study Design
This is a Phase 1, open-label, dose-escalation (3+3 design, intra-subject dose escalation) study in which eligible subjects were treated with dasatinib orally once daily until refractory disease progression, intolerable toxicity, or patient/physician preference. Dasatinib was continued as long as clinical benefit was maintained.

Three strata were defined as follows:

- Stratum 1: imatinib-resistant or imatinib-intolerant Philadelphia chromosome-positive (Ph+) CML in chronic phase
- Stratum 2/3:
  - Imatinib resistant or imatinib-intolerant Ph+ CML in accelerated phase, or in myeloid blast phase (MBP) or lymphoid blast phase (LBP)
  - Relapsed or refractory Ph+ ALL after imatinib
  - Second or subsequent relapse of Ph+ AML
- Stratum 4: second or subsequent relapse of Philadelphia chromosome-negative (Ph-) ALL or Ph- AML

Intra-subject dose escalation was based on tolerance and on individual response.

Treatment courses were defined as 3 weeks (21 days plus any required delay). For subjects who stayed on treatment longer than 12 months, courses after 12 months were defined in quartiles of 13 weeks. Subjects were to be followed until death or up to 5 years after the end of treatment.

Study Treatment
The starting dose for all strata was 60 mg/m2 orally once daily. Dose escalations were made in increments of 20-33%. Tablets of 5 mg, 20 mg and 50 mg were supplied and individual doses were rounded to the nearest 5 mg. Dose was recalculated based on body surface area (BSA) every 12 weeks, or more often if needed. The table below provides the dose levels used for escalation of the starting dose on a per stratum-basis and for intra-subject dose escalation.

Table 8. Dasatinib Dosing

Dose Level	Dose
-1	50 mg/m^2 daily (-17%)
1	60 mg/m^2 daily (starting dose)
2	80 mg/m^2 daily (+33%)
3	100 mg/m^2 daily (+25%)
4	120 mg/m^2 daily (+20%)

Source: FDA Clinical Reviewer adapted from Study CA180018 CSR

Dasatinib was administered daily for as long as clinical benefit was maintained.

Reviewer Comment: The remainder of this review of Study CA180018 will focus only information, data and results from Stratum 1, the relevant patient population for this application.

Objectives

Primary: To establish, by stratum using a dose-finding design, a recommended Phase 2 dose of dasatinib in children and adolescents with relapsed or refractory leukemia.

Secondary:

- Determine the adverse events (AEs) and identify any dose-limiting toxicities (DLTs) of dasatinib in children and adolescents with Ph+ CP-CML (stratum 1)
- To estimate, by stratum the rates of morphologic (major hematologic response [MaHR]), cytogenetic (major cytogenetic response [MCyR]), and molecular (quantitative PCR) responses to dasatinib
- To describe, by stratum, time to response, response duration, PFS, and survival of children and adolescents with relapsed or refractory leukemia treated with dasatinib
- To estimate, as a function of dasatinib dose, plasma and (if applicable) CSF PK parameters of dasatinib
- To describe the spectrum of mutations in the BCR-ABL gene (Strata 1 and 2/3) and in the FLT3 and KIT genes (Stratum 4) at baseline and at the end of treatment, and to explore the role of mutations as predictors of response.

Patient Population

The overall study population included children and adolescents ≥1 to <21 years of age, with Ph+ CML in chronic, accelerated, or blast phase, resistant or intolerant to imatinib, or in first or subsequent relapse of Ph+ ALL or Ph+ AML after prior imatinib, or in second or subsequent relapse of Ph-ALL or AML.

Stratum 1: CP-CML, defined as:

- <15% blasts in the peripheral blood (PB) and in bone marrow (BM)
- <20% basophils in PB
- <30% blasts + promyelocytes in PB and in BM
- Platelets ≥ 100,000/mm^3 unless thrombocytopenia is due to recent therapy

- No extramedullary involvement (other than liver or spleen)
- Note: subjects who had previously met the criteria for AP or BP-CML, then responded, and met the criteria for CP-CML were not eligible for Stratum 1.

Inclusion Criteria

- Diagnosis – Stratum 1: Ph+ CML in CP with resistant or progressive disease during, or intolerance to, imatinib, including:
  - Failure to achieve, or loss of, complete hematologic response (CHR) after ≥ 3 months of imatinib
  - Failure to achieve MCyR (≤ 35% Ph+ metaphases) after ≥ 6 months or CCyR (0% Ph+ metaphases) after ≥ 12 months of imatinib
  - Recurrence of Ph+ clone with >35% abnormal metaphases after prior MCyR to imatinib
  - Increase in BCR-ABL signal by quantitative PCR of ≥ 1 log, confirmed at ≥ 6 week interval (must have been discussed with the Principal Investigator)
- Age ≥ 1 and < 21 years
- Lansky or Karnofsky scale ≥ 60
- Life expectancy > 3 weeks
- Serum calcium levels above LLN; sodium, potassium, magnesium, phosphorus, AST, ALT and bilirubin ≤ Grade 1; Bun and creatinine ≤ Grade 2
- No organ toxicity ≥ Grade 2 (except alopecia), and recovered from acute toxicity of previous therapy
- Able to comply with scheduled follow up at one of the centers involved in this study
- Women of childbearing potential must have had a negative serum or urine pregnancy test within 72 hours prior to the start of study medication, and must have been using an adequate method of contraception to avoid pregnancy throughout the study and for up to 3 months after the study in such a manner that the risk of pregnancy was minimized
- Written informed consent from subject or from parents/legal guardians for minor subjects

Exclusion Criteria

- Subjects for whom potentially curative therapy was available, including immediate stem-cell transplantation. Subjects in Stratum 1 were to have had an ongoing identical HLA donor search and may have discontinued study if a donor became available
- Subjects with symptomatic extramedullary leukemia (i.e. clinical symptoms such as convulsions due to CNS disease)
- Any serious uncontrolled medical disorder that impaired the ability of the subject to receive protocol therapy, including:
  - Ongoing uncontrolled infection
  - Not recovered from acute toxicity of previous therapy
  - Clinically significant disorder of platelet function or ongoing GI bleeding

  - Clinically significant cardiovascular disease, congenital long QT syndrome, history of ventricular arrhythmias or heart block, or prolonged corrected QT interval > 450 ms on baseline ECG
- Expected noncompliance, or unable to have regular follow-up due to psychological, social, familial or geographic reasons
- Subjects who received:
  - Any investigational agent or any other anti-cancer agent within 14 days prior to treatment start. Imatinib may have been continued up to 7 days before treatment start, or, in the presence of rising peripheral blast cells, imatinib may have been continued up to 2 days before treatment start.
  - Any prior therapy with dasatinib
- Subjects requiring ongoing medications, which:
  - Irreversibly inhibit platelet function or anticoagulants
  - Known risk of causing QTc prolongation
- Women of child bearing potential with a positive pregnancy test prior to study drug administration, or who were unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period and for up to 3 months after the study, or who were pregnant or breastfeeding.
- Prisoners or subjects who were compulsorily detained for treatment of either a psychiatric or physical illness.

Schedule of Assessments
An overview of the schedule of assessments on treatment and at follow-up is provided in the table below.

Table 9. CA180018 - Treatment and Follow-Up Procedures

Procedures	Course							EOT	FU	Comment
	1	2	3, 4	5	6, 7, 8	9	10+			
AEs; concomitant medication: transfusions	X	X	X	X	X	X	X	X		
Physical Examination	X	X	X	X	X	X	X	X	X	Every 4 courses; every quarter after 12 months of trtm. FU: every 6 mos during FU yr 1 & 2, yearly thereafter.
Weight, Vital Signs, Performance Status	X	X	X	X	X	X	X	X		Every quarter after 12 mos of trtm
Extramedullary Involvement	X	X	X	X	X	X	X	X		
Pregnancy Test				X		X	X	X		Every 4 courses (if clinically indicated) during first 12 mos of trtm and at every course > 12 mos of trtm.
Chest X-ray				X		X		X		If normal at C05 and C09, subsequent assessment at discretion of Investigator
Echocardiogram or MUGA scan	X			X				X		Within 1st mo, after course 4, then every 6 mos while on trtm and in case of heart failure
ECG	X							X		On day 10±2 of C01; on day 10±2 after dose escalation
Efficacy Data										
Progression; best hematologic/ cytogenetic/ molecular response								X		
Therapy for Leukemia; Radiotherapy; Stem Cell transplant									X	To be assessed quarterly/yearly
Follow-Up assessment of progression, status, and survival									X	
Chemistry panel	X	X	X	X	X	X	X	X	X	If normal at C02 and C03, required every 4 courses only; every quarter after 12 mos of trtm, every 6 mos after 24 mos of trtm. FU: yearly

Procedures	Course							EOT	FU	Comment
	1	2	3, 4	5	6, 7, 8	9	10+			
CBC, Differential & Platelets	X	X	X	X	X	X	X	X		Wkly assessments during first 6 wks; every quarter after 12 mos of trtm
BMA and peripheral blood samples for morphology, qPCR cytogenetics, and blood sample for mutation analysis	→	→	→	→	→	→	→	→	→	See Table 3.5.1D for details of BM and PB sample procurement
PK sampling	X									During wk 1 of C01 and as soon as possible after dose escalation (see separate table)
CSF cell count & Cytopathology	X	X								CSF analysis, baseline only required in strata 1 and 2/3
Growth & Development										
Height & Weight with Growth curve							X		X	During trtm: at mo 12 and yearly thereafter. FU: yearly
Bone age, Pubertal Status (Tanner stage)							X		X	During trtm: mo 12 and yearly thereafter. FU: yearly for subjects with significant growth deceleration
T-4, TSH; FSH, LH for pubertal children; IGF-1, IGF beta-3							X		X	FU: yearly assessments for subjects with significant growth deceleration
Bone mineral metabolism										
Bone mineral density							X		X	During trtm: at mo 12 and yearly thereafter. FU: yearly
History of bone fractures									X	Yearly during FU
Urinary-N-telopeptide, Bone Alkaline Phosphatase							X		X	During trtm: at mo 12 and yearly thereafter. FU: yearly

AEs - adverse events, BMA - bone marrow aspirate, CBC - complete blood count, CSF - cerebral spinal fluid, ECG - electrocardiogram, FSH - follicle stimulating hormone, FU - follow-up, IGF - insulin-like growth factor, IGF beta-3 - insulin-like growth factor binding protein-3, LH - luteinizing hormone, mo - month, MUGA - multigated acquisition scan, PK - pharmacokinetics, Trtm - treatment, TSH - thyroid stimulating hormone, wk - week

Courses (C01, C02, etc.) are defined as 3 weeks during the first 12 months of treatment and as one quartile (13 weeks) afterwards.

Source: CA180018 CSR, Table 3.4.1B

Collection of Adverse Events

Adverse events were assessed continuously and graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Safety analyses included

frequency, severity and relatedness of all AEs, abnormal laboratory values, use of concomitant medications, and dose interruptions or reductions.

Dose Modifications for Toxicity

Non-Hematologic Toxicity:

- For Grade 2 non-hematologic toxicity: Treatment may be interrupted until toxicity decreases to ≤ Grade 1. Dasatinib may be reinitiated at the original dose. If the same toxicity recurs at Grade 2 on re-treatment, treatment will again be interrupted until the toxicity decreases to ≤ grade 1 and dasatinib may then be restarted at the next lower dose level. If the same Grade 2 non-hematologic toxicity recurs in spite of this dose reduction, a second dose reduction is permitted.
- For Grade 3 non-hematologic toxicity: Treatment may be interrupted until the toxicity decreases to ≤ Grade 1 (or to Grade 2 if that was baseline). Dasatinib may then be reinitiated at the next lower dose level. For clinically-manageable toxicities such as vomiting or diarrhea, the same dasatinib dose may be restarted under maximized medical coverage. If the same toxicity reoccurs in spite of adequate supportive intervention, the dose should be reduced. If the same toxicity recurs at Grade 3 in spite of dose reduction, one additional dose reduction is permitted. If the same Grade 3 toxicity reoccurs in spite of a second dose reduction, dasatinib should be discontinued.
- For Grade 3 major organ toxicity (CNS, cardiac, pulmonary or renal), the dose may be reduced by two levels.
- For Grade 4 non-hematologic toxicity related to dasatinib, subjects should generally discontinue dasatinib therapy. Following resolution of Grade 4 toxicity to ≤ Grade 1 (or to baseline) dasatinib may be given with two-dose-level reduction if in the best interest of the subject.
- Subjects with QTc > 450 msec should be discontinued from study therapy unless the subject is clearly benefiting as determined by the Investigator and a dose reduction is considered in the subject's best interest after written Sponsor agreement.

Hematologic Toxicity:

- No dose reductions or treatment interruptions during the first 3 weeks of therapy for cytopenias or for febrile neutropenia.
- If Grade 4 neutropenia or thrombocytopenia persists after 3 weeks of treatment, bone marrow aspirate should be performed as often as every 3 weeks to permit decision making.
- In cases of complete tumor clearance, dasatinib will be delayed until ANC >1000/mm^3 and platelets >20,000/mm^3, at which time treatment may be resumed at full dose or with 1 dose level reduction at Investigator's discretion. If Grade 4 neutropenia or thrombocytopenia recur during CHR, study drug will be delayed and subsequently resumed at 1 lower dose level.

Intra-patient Dose Escalation
Intra-patient dose-escalation was determined by the Investigator in consultation with Principal Investigator, and was recommended, but not required.

Statistical Plan
The sample size was not empirically derived, but was determined based on the feasibility of accrual and on the dose levels used for the escalations of the starting dose. In Stratum 1, at least 12 subjects were to be treated to meet the primary objective (6 subjects at the 60 mg/m^2 starting dose; and 6 subjects at the 80 mg/m^2 starting dose, unless there was excessive toxicity at either dose, or no clinical need to escalate to 80 mg/m^2). Up to additional 4 subjects were to be treated at the 60 mg/m^2 dose level in Stratum 1 to expand the number of subjects at the dose level selected for the Phase 2 study.

Dose escalation was based on the tolerability at a given dose level and the clinical efficacy at a given dose. The recommended Phase 2 dose was determined based on the aggregation of safety data for these strata, and an assessment of safety at a minimum of 2 dose levels was planned. Best on-study hematologic, cytogenetic and molecular response rates including key efficacy endpoints were estimated using all treated subjects by stratum and by dose cohort. Ninety-five percent exact confidence intervals (CIs) using the method of Clopper and Pearson were provided for rates computed on the recommended Phase 2 dose.

Kaplan-Meier plots for PFS, overall survival (OS), duration and time to response by stratum were planned and provided. A 2-sided, 95% CI for the median was computed using the method of Brookmeyer and Crowley.

Analysis Populations
- Enrolled: All subjects who signed the informed consent form
- Treated subjects: All subjects how received at least one dose of dasatinib. Used for baseline characteristics, safety and efficacy analyses.
- PK Data Set: All available derived PK parameter values were included in the PK datasets and reported, but only subjects with adequate PK profiles were included in the summary statistics and statistical analysis.
- Mutation Data Set: All available mutation data from subjects who received dasatinib.
- Molecular Data Set: Subjects with BCR-ABL quantification data (PCR).

Key Protocol Revisions
A summary of protocol revisions/amendments is provided in the table below.

Table 10. CA180018 - Protocol Revisions

Amendment and Date	Summary of Major Changes
Amendment 1 July 6, 2006	- Delete references throughout the protocol to PD assays and central morphology review of BM smears, which were not performed in this trial. - Correct primary efficacy endpoint from CHR to MaHR in Strata 2-4 - Specify that mutation analysis will be done in all strata - Add moderate neutropenia (ANC 500-1,000) to the definition of CHR for consistency with other dasatinib studies - Specify definitions of imatinib resistance and imatinib intolerance
Amendment 2 December 6, 2007	- Update the Study Medical Monitor and Director - Elimination of previous stratum 3 (AP and BP CML or Ph+ AML in ≥ 2nd relapse) and incorporate previous strata 2 and 3 into a new stratum (2/3) - Add additional data from an ongoing Phase 1 study in pediatric patients with relapsed/refractory solid tumors or imatinib resistant Ph+ leukemias, and an adult Phase 2 breast cancer trial to provide an update when using dasatinib at doses ≥ 120 mg/m^2 daily. - All extramedullary disease - Clarify the PD secondary objectives - Clarify that confirmation of hematologic response must occur at least 4 weeks after it is first documented and clarify complete hematologic response - Clarification of the preparation of an oral solution of dasatinib and of the "handling and dispensing of investigational product".
Amendment 3 June 24, 2008	- To open the study to participation of clinical sites outside of the ITCC consortium - Updated Medical Monitor, contact details of coordinating investigator and description of investigational product - Added additional detail regarding collection of peripheral blood and bone marrow aspirate samples - Updated protocol language and removed typographical errors.

Amendment 4 November 18, 2008	- Clarify that this study will not proceed to its planned phase 2 component. - Change of study phase from Phase 1/2 to Phase 1 - Allow for the collection of additional safety and efficacy data for the doses that will be used in the phase 2 study (CA180226). - Clarification of per-stratum use of dose levels both for starting doses and for intra-patient dose escalations - Adjustment of patient numbers that will be accrued per stratum - Change in duration and content of follow-up period
Amendment 5 December 8, 2009	- Add tests to monitor growth and development and bone metabolism during the treatment period and for up to 5 years follow up after study drug administration. - Implement a modified visit schedule for study subjects who are on treatment for more than 12 months - Update maximum treatment duration - Amend visit schedule for study subjects after 12 months of treatment.

Source: FDA Clinical Reviewer, Adapted from Study CA180018 CSR

Results

Demographics

A total of 63 subjects were enrolled and 58 were treated with dasatinib and were evaluable for the primary endpoint (selection of the Phase 2 dose)

- Stratum 1 (Ph+ CP-CML): 17
- Stratum 2/3 (Ph+ AP-CML, Ph+ BP-CML, Ph+ ALL): 17
- Stratum 4 (Ph- AML, Ph- ALL): 24

The median age of the entire study population was 10 years (range: 1.3 – 21.0). An overview of the demographic information for subjects enrolled on Cohort 1of this study is provided in the tables below.

Table 11. Study CA180018 Stratum 1 - Baseline Demographics

Parameter	Total (N=17)
Age (years)	
Median	13.0
Range	4.0 – 17.0
Age Category (%)	
< 2 years	0
2 – 6 years	2 (11.8)
7 – 11 years	6 (35.3)
12 -18 years	9 (52.9)
Gender, n(%)	
Male	11 (64.7)
Female	6 (35.3)
Race, n(%)	
White	16 (94.1)
Black/African American	0
Asian	1 (5.9)
Other	0

Source: FDA Clinical Reviewer, Adapted from Study CA180018 CSR

Baseline hematologic disease status for each stratum was consistent with the baseline type of leukemia. The median WBC, platelet count and percentage of blasts in the bone marrow are presented in the table below.

Table 12. Study CA180018 Stratum 1 - Baseline Hematologic Parameters

	Median (range)
WBC	8.7/mm^3 (3.6 – 134.6/mm^3)
Platelet	294,000/mm^3 (139,000 – 1,058,000/mm^3)
Bone Marrow Blasts	0% (0% - 4%)

Source: Study CA180018 CSR

Subject Disposition
A total of 18 subjects were enrolled in Stratum 1 and 17 were treated with dasatinib. At the time of data cutoff, six subjects were still receiving study drug. An overview of the disposition for subjects enrolled in Cohort 1 and the reasons for treatment discontinuation is provided in the table below.

Table 13. Study CA180018 Stratum 1 - Subject Disposition

	Stratum 1 n (%)
Enrolled	18 (100.0)
Treated	17 (94.4)*
Still on Treatment	6 (35.3)
Discontinued Treatment	11 (64.7)
Reason for Discontinuation	
Resistant Disease	1 (5.9)
Refractory Disease	1 (5.9)
Decision to undergo stem cell transplant	6 (35.3)
Study drug toxicity	0
Subject Request	1 (5.9)
Other	2 (11.8)

* One subject was enrolled, but did not meet criteria for treatment due to decreased BCR-ABL levels in screening bone marrow
Source: FDA Clinical Reviewer Analysis

5.3.2 Study CA180226

Study Title: A phase 2 study of dasatinib therapy in children and adolescents with newly diagnosed chronic phase chronic myelogenous leukemia or with Ph+ leukemias resistant or intolerant to imatinib.

Study Period: March 18, 2009 – Ongoing (Database lock: November 4, 2016)

Clinical Sites: 80 sites in 18 countries worldwide.

Study Design
This was a Phase 2, open-label, non-randomized, multi-center trial in pediatric patients age 0 to 18 years with newly diagnosed CML who were treatment-naive and with CP-CML, Ph+ ALL or with AP-CML or BPCML, who relapsed after, or were resistant or intolerant to imatinib. This study enrolled subjects on 3 cohorts based on underlying disease and prior treatment, as follows:

- Cohort 1: Ph+ CP-CML with resistance or intolerance to imatinib
- Cohort 2: AP/BP-CML or Ph+ ALL with resistance or intolerance to imatinib
- Cohort 3: Newly diagnosed Ph+ CP-CML

Cohort 3 was further divided into 2 subgroups:

- Cohort 3a: Tablet formulation
- Cohort 3b: PFOS formulation

All subjects received dasatinib orally once daily until disease progression, intolerable toxicity, or subject/physician preference. Subjects in all cohorts were treated for a minimum of 24 months. After 24 months of treatment, subjects who completed the study and continued to demonstrate clinical benefit were eligible to receive study drug up to 12 months after the approval of study drug within the pediatric population by the responsible health authority for the indication under study or until the study drug was commercially available within that country, whichever occurs sooner. Efficacy was assessed by cohort and sub-cohort for all treated subjects. Safety of dasatinib was reported for all treated subjects. Dose reductions were performed for excess toxicity. All subjects who discontinued study therapy were to be followed yearly for survival for up to 5 years after treatment discontinuation. Study therapy was discontinued at any time in case of disease progression or unacceptable toxicity.

The planned enrollment for this study was at least 105 subjects with Ph+ CP-CML (25 with prior imatinib treatment and 80 treatment-naive subjects) and 17 subjects with Ph+ ALL, AP-CML or BP-CML (of whom 8 subjects in Cohort 2 are advanced phase CML either accelerated or blast phase). Thus, a minimum of 122 treated subjects were expected in total.

Clinical Reviewer Comment: The remainder of this review of Study CA180226 will focus only on the information, data and results from Cohort 1 and Cohort 3, the relevant patient populations for this application. (b) (4)

(b) (4)

Study Treatment

- Cohort 1: Dasatinib 60 mg/m^2 once daily (maximum dose of 100 mg daily for subjects with high BSA)
- Cohort 3a: Dasatinib tablets 60 mg/m^2 once daily
- Cohort 3b: Dasatinib PFOS 72 mg/m^2 once daily.

Dasatinib was administered orally on a once daily schedule. Tablets of 5, 20, and 50 mg or dasatinib PFOS (oral suspension constituted with water) were used. Individual doses were rounded to the nearest 5 mg (up or down). The dose was recalculated based on BSA every 12 weeks, or more often if necessary.

Clinical Reviewer Comment: (b) (4)

Objectives

Primary Objectives:

- To estimate the major cytogenetic response (MCyR) rate to dasatinib therapy in children and adolescents with CP-CML who proved resistant to or intolerant of imatinib (Cohort 1).
  - The rate of MCyR as defined as complete (0%) or partial (1-35%) of Ph+ metaphases in at least 20 metaphases in the bone marrow.
- To estimate the complete hematologic response (CHR) rate in children and adolescents with Ph+ ALL, AP-CML and BP CML who were resistant to, intolerant to, or who relapsed after prior imatinib therapy (Cohort 2).
  - The rate of CHR including no more than 5% blasts in the bone marrow and normal WBC without blasts in the peripheral blood
- To estimate the complete cytogenetic response (CCyR) rate to dasatinib therapy in children and adolescents with newly diagnosed CP-CML who are treatment naïve (except hydroxyurea) (Cohort 3).

Secondary Objectives

- To assess the safety and tolerability of dasatinib in children and adolescents treated with dasatinib for relapsed or refractory Ph+ leukemias.
- To assess the safety and tolerability of dasatinib in children and adolescents with newly diagnosed Ph+ CP-CML who are treatment naïve.
- To evaluate additional measures of efficacy in children and adolescents with newly diagnosed CP-CML or subjects with relapsed or refractory Ph+ leukemias treated on a given regimen of dasatinib including:
  - Duration and time to MCyR and CHR
  - Progression-free survival, disease-free survival and overall survival
  - Rates of MCyR, best cytogenetic response, CHR and molecular response (assessed by quantitative PCR).
- To describe the spectrum of the BCR-ABL mutations at baseline, at progression, treatment failure, or end of treatment, and to explore the role of mutations as predictors of response.

Exploratory Objectives

- To describe growth and development and bone mineral content
- To assess the PK of dasatinib following oral administration of dasatinib PFOS in Cohort 3b.

Patient Population

- Cohort 1: Subjects must have Ph+ CML in CP, defined by the presence of all of the following:
  - <15% blasts in peripheral blood and bone marrow
  - <20% basophils in peripheral blood
  - <30% blasts + promyelocytes in peripheral blood and bone marrow

- Platelets ≥ 100 x 10^9/L unless thrombocytopenia secondary to recent treatment
- No extramedullary involvement other than liver and/or spleen
- Ph+ (with 9:22 translocation) must be demonstrated by bone marrow cytogenetics
- Resistant or intolerant to imatinib, defined by at least 1 of the following criteria:
  - Failure to achieve, or loss of, CHR after ≥ 3 months of imatinib at a daily dose of 260 mg/m^2 or greater
  - Failure to achieve MCyR after ≥ 6 months of imatinib therapy at a daily dose of 260 mg/m^2 or greater
  - Failure to achieve CCyR after ≥ 12 months of imatinib therapy at a daily dose of 260 mg/m^2 or greater
  - Absolute increase of ≥ 30% of the percentage of Ph+ metaphases, confirmed at 2-4 weeks, after prior MCyR to imatinib at a daily dose of 260 mg/m^2 or greater

Note: Subjects who previously met the criteria for AP or BP CML, then responded and now meet the criteria for CP CML are not eligible for Cohort 1.

- Cohort 3: Subjects must have been newly diagnosed with Ph+ CML in CP, defined by the presence of all of the following:
  - <15% blasts in peripheral blood and bone marrow
  - <20% basophils in peripheral blood
  - <30% blasts + promyelocytes in peripheral blood and bone marrow
  - Platelets ≥ 100 x 109/L unless thrombocytopenia secondary to recent treatment
  - No extramedullary involvement other than liver and/or spleen
  - Ph+ (with 9:22 translocation) must be demonstrated by bone marrow cytogenetics

Inclusion Criteria

- Signed written informed consent
- Age 0 to 18 years
- Lansky or Karnofsky scale > 50
- Life expectancy ≥ 12 weeks
- Must have recovered to baseline or Grade 1 from previous toxicities (except alopecia) resulting from recent therapies, including chemotherapy, hormonal therapy, immunotherapy, biological therapy or investigational product and radiation therapy.
- Serum sodium, bicarbonate, phosphorus and calcium levels ≤ Grade 1 and adequate hepatic and renal function defined as AST, ALT, bilirubin and creatinine ≤ Grade 2
- Women of childbearing potential must have a negative serum or urine pregnancy test within 24 hours prior to the start of study drug. Must agree to follow instructions

for methods of contraception starting at the time of enrollment for the duration of treatment with study drug plus 30 days post-treatment completion.
- Men who are sexually active with women of childbearing potential must agree to follow instructions for methods of contraception for the duration of treatment with the study drug and for 90 days post-treatment completion.

Exclusion Criteria:
- Women of childbearing potential who are unwilling or unable to use a highly effective method to avoid pregnancy for the entire study period and for up to 1 month after the last dose of investigational product
- Women who are pregnant or breastfeeding, or likely to become pregnant
- Subjects for whom potentially curative therapy is available, including HSCT at the time of assessment for enrollment
- Subjects with isolated CNS disease
  - Subjects with CNS1, CNS2 and CNS3 disease are eligible for the study provided this is a combined relapse which also involves the bone marrow in addition to CNS and they are asymptomatic from their CNS disease.
- Isolated extramedullary disease with <5% blasts in bone marrow
- Any serious uncontrolled medical disorder that would impair the ability of the subject to receive protocol therapy, including:
  - Ongoing uncontrolled infection
  - Clinically significant disorder of platelet function
  - Clinically significant cardiovascular disease, congenital long QT syndrome, history of ventricular arrhythmia or heart block, prolonged QTc >450 ms on baseline ECT
  - Subjects diagnosed with T315I mutation
  - Subjects who have experienced hypersensitivity to dasatinib or to any of the excipients.
  - Subjects with hereditary problems of galactose intolerance or Lapp lactase deficiency or glucose-galactose malabsorption
  - Uncorrected hypokalemia or hypomagnesemia
- Expected non-compliance to protocol schedule or unable to have regular follow-up due to psychological, social, familial or geographic reasons
- Prisoners or subjects who are involuntarily incarcerated
- Subjects who are compulsorily detained for treatment of either a psychiatric or physical illness

Schedule of Assessments

An overview of the schedule of assessments on treatment is provided in the table below.

Table 14. Study CA180226 - Schedule of Assessments

		On Treatment Visits[a]																
		Weeks							Months									
Procedure	Pre-Treatment	1	2	3	4	5	6	8	3	4	5	6	9	12	15	18	21	24	Post Month 24
Eligibility Assessments																			
Informed Consent	X																		
Medical History and Inclusion/ Exclusion Criteria	X																		
Pregnancy Test[b]	X[c]				X			X	X	X	X	X	X	X	X	X	X	X	Every month
Safety Assessments																			
Assessment of Signs/Symptoms and AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination and Vital Signs[e]	X	X[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Every 3 months
Review Contraceptive Requirements for subjects of child bearing potential and male subjects		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	At each visit

		On Treatment Visits[a]																
		Weeks							Months									
Procedure	**Pre-Treatment**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**3**	**4**	**5**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**Post Month 24**
Extramedullary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Every 3 months
Molecular Analysis	X								X			X	X	X	X	X	X	X	Every 6 months
Mutation Analysis	X																		
Chest X-Ray[h]	X																		
12-Lead ECG[i]	X		X											X[i]				X[i]	Yearly[i]
Echocardiogram[h]	X													X[h]				X[h]	Yearly[h]
CSF cell count and cytopathology[j]	X																		
Serologic Testing for Hepatitis B[k]																			
Laboratory Assessments - Cohort #1																			
CBC, differential and platelets	X[c]	X[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Every 3 months
Serum Chemistry[m]	X[c]		X		X		X	X	X	X	X	X	X	X	X	X	X	X	Every 6 months

		On Treatment Visits[a]																
		Weeks							Months									
Procedure	**Pre-Treatment**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**3**	**4**	**5**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**Post Month 24**
Bone Marrow Aspirate for morphology and cytogenetics[o]	X[p]								X			X	X	X	X	X	X	X	Yearly
Laboratory Assessments - Cohort #2																			
CBC, differential and platelets	X[c]	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Every 3 months
Serum Chemistry[m]	X[c]	Daily	Twice in Wk 2[q]		X		X	X	X	X	X	X	X	X	X	X	X	X	Every 6 months
Bone Marrow Aspirate for morphology and cytogenetics[o]	X[p]								X			X	X	X	X	X	X	X	Yearly
Laboratory Assessments - Cohort #3																			
CBC, differential and platelets	X[c]	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Every 3 months
Serum Chemistry[m]	X[c]		X		X		X	X	X	X	X	X	X	X	X	X	X	X	Every 6 months

		On Treatment Visits[a]																
		Weeks							Months									
Procedure	**Pre-Treatment**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**3**	**4**	**5**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**Post Month 24**
Bone Marrow Aspirate for morphology and cytogenetics[o]	X[p]								X			X	X[r]	X	X[r]	X[r]	X[r]	X	Yearly
Pharmacokinetics - Sub-cohort 3b		X	X	X															
Palatability - Sub-cohort 3b		X	X	X	X														
Follow-Up All Subjects																			
Long-term Growth and Development Assessments																			
Height/weight	X													X				X	Yearly
Bone Age Evaluation	X													X				X	Yearly
Tanner Stage	X													X				X	Yearly
Labs: freeT4, TSH, FSH((ages ≥ 8 years), LH (ages ≥ 8 years) IGF-1, IGFB-3	X													X				X	Yearly

		On Treatment Visits[a]																
		Weeks							Months									
Procedure	Pre-Treatment	1	2	3	4	5	6	8	3	4	5	6	9	12	15	18	21	24	Post Month 24
Long-term Bone Metabolism Assessments																			
DXA[t]	X													X				X	Yearly
Urinary N-Teleopeptide	X													X				X	Yearly
Bone Alkaline Phosphatase	X													X				X	Yearly
All Subjects																			
Assessment of survival																			

Source: Study CA180226 CSR

Collection of Adverse Events
Adverse events were assessed continuously and graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Safety analyses included frequency, severity and relatedness of all AEs, abnormal laboratory values, use of concomitant medications, and dose interruptions or reductions.

Dose Modifications for Toxicity:
The dose of dasatinib was reduced in the case of excessive toxicity.

Non-Hematologic Toxicity:
Dose reductions for non-hematologic toxicity are outlined in the table below.

Table 15. Study CA180226 - Dose Reductions for Non-Hematologic Toxicity

Toxicity	Occurrence	Dasatinib
Grade 2 and related	1st occurrence	Hold therapy and resume at the same dose after recovery to ≤ Grade 1
	2nd/3rd occurrence	Hold therapy and resume at the next lower dose level after recovery to ≤ Grade 1
	4th occurrence	Consider discontinuing therapy
Grade 3 related clinically manageable toxicity such as vomiting or diarrhea	1st occurrence	Hold therapy and resume at the same dose after recovery to ≤ Grade 1
	2nd/3rd occurrence	Hold therapy and resume at the next lower dose level after recovery to ≤ Grade 1
	4th occurrence	Discontinue therapy
Grade 3 and related[a]	1st/2nd occurrence	Hold therapy and resume at the next lower level after recovery to ≤ Grade 1 or baseline.
	3rd occurence	Discontinue therapy
Grade 4 and related	1st occurrence	Select best interest for subject: - Hold therapy and resume with two-dose-level reduction after recovery to ≤ Grade 1 or baseline; Or - discontinue therapy
QTc >530 msec (Fridericia correction)	Any occurrence	Select best interest for subject: - Discontinue therapy Or - Dose reduction after written Sponsor agreement

[a] For Grade 3 major organ toxicity (CNS, cardiac, pulmonary, renal), the dose may be reduced by two levels.
Source: Study CA180226 CSR

Hematologic Toxicity

Temporary dose interruption, reduction or treatment discontinuation was based on the individual subject's disease and response. For all subjects, if Grade ≥ 3 neutropenia or thrombocytopenia recurs during CHR, study drug was interrupted and subsequently resumed at 1 lower dose level. Temporary dose reductions for intermediate degrees of cytopenias and disease response were at the Investigator's discretion. If Grade ≥ 3 neutropenia or thrombocytopenia persists for more than 3 weeks on study, BMA was performed as often as every 3 weeks to assist decision making. In cases of complete tumor clearance (bone marrow hypocellular and blasts < 5%), dasatinib was delayed until ANC > 1,000/mm^3, and platelets > 75,000/mm^3 at which time treatment could have been resumed at full dose or with one dose level reduction at Investigator's discretion.

Dose levels for treatment modifications are provided in the table below.

Table 16. Study CA180226 - Dose Modification Levels

	Cohort-#1 and Cohort #3	**Cohort 3b and PFOS**
Escalation (+1)	80 mg/m^2 QD With a maximum dose of 120 mg QD	96 mg/m2 QD With a maximum dose of 140 mg QD
Starting Dose	**60 mg/m^2 QD** With a maximum dose of 100 mg QD	**72 mg/m2 QD** **With a maximum dose of 120 mg QD**
Reduction (-1)	50 mg/m^2 QD With a maximum dose of 80 mg QD	60 mg/m2 QD With a maximum dose of 100 mg QD
Reduction (-2)	40 mg/m^2 QD With a maximum dose of 60 mg QD	48 mg/m2 QD With a maximum dose of 80 mg QD

Source: Study CA180226 CSR

Statistical Plan

Sample Size

The study was designed to enroll and treat at least 25 subjects in Cohort 1, 34 subjects in Cohort 2, 50 subjects in sub-cohort 3a, and 30 subjects in sub-cohort 3b.

Cohort 1: A response rate in excess of 30% for MCyR was considered of clinical interest. The study design tested the null hypothesis that the true MCyR rate was less than or equal to 30% versus the alternative hypothesis that it exceeded 30%. The one-sided type I error rate was 2.5% and assuming a 60% true MCyR rate (30% more than the response rate under the null hypothesis), 25 response-evaluable subjects were required to have at least 84% power to reject the null hypothesis. The drug was considered of clinical interest if there were 13 or more responders out of the total of 25 response evaluable subjects.

Cohort 3: A response rate in excess of 55% for CCyR was considered of clinical interest. The study design tested the null hypothesis that the true CCyR rate was less than or equal to 55% versus the alternative hypothesis that it exceeded 55%. The one-sided type I error rate was 2.5% and assuming a 75% true CCyR rate among newly diagnosed subjects with CP CML (20% more than the response rate under the null hypothesis), 50 response-evaluable subjects in Cohort 3a yielded 83% power to reject the null hypothesis. The drug was considered of clinical interest if there were 35 or more responders out of the total of 50 response evaluable subjects.

A minimum of 30 subjects in Cohort 3b were administered PFOS. The proposed PK sampling design in 30 subjects provided an adequate estimate of PK parameters, such that the 95% CI of clearance (CL/F) and volume of distribution (VC/F) are within 60% and 140% of the geometric mean estimate across pediatric sub-groups (body weight 10 to 100 kg).

Analysis Populations

- Treated Subjects: All subjects who received at least one dose of dasatinib. Demographic, baseline characteristics, safety and efficacy analyses were performed on all treated subjects.
- Mutation Data Set: All available mutation data from subjects who received dasatinib
- PK Data Set: All available PK data from subjects in Cohort 3b who received dasatinib PFOS.

Statistical Analyses

Response rates of major cytogenetic response, complete hematologic response, and complete cytogenetic response were presented with their 95% exact confidence intervals for each cohort. Similar presentations were made for secondary response rate endpoints. The time-to-event endpoints were assessed by Kaplan-Meier estimates and graphs.

Key Protocol Revisions

A summary of key protocol revisions/amendments is provided in the table below.

Table 17. Study CA180226 - Key Protocol Revisions

Amendment and Date	Summary of Major Changes
Amendment 3 December 17, 2009	- The protocol was revised to include a new cohort of pediatric subjects with newly diagnosed treatment-naïve CP-CML (Cohort 3) - Expand the primary objective to include Cohort 3 - Clarify study duration - Establish data monitoring committee (DMC) - Addition of yearly ECGs - Clarify inclusion criteria - Update exclusion criteria to exclude patients with the T315I

	mutation and patients with galactose intolerance and glucose-galactose malabsorption. - Clarify mode of drug administration - Synchronize visit and assessment schedules - Change the molecular analysis schedule to coincide with scheduled visits - All long-term follow up plan
Amendment 7 October 4, 2010	- Provide updated information regarding the use of dasatinib for first line treatment in adults with CP-CML as further justification to study the same patient population in pediatric subjects. - Revised estimated number of sites - Clarified diagnosis criteria for Cohort 2 - Separated diagnosis criteria for Cohort 3 for clarity - Revised resistance criteria to cap previous imatinib dose at 400 mg/day for subjects with high BSAs
Amendment 3 June 24, 2008	- To open the study to participation of clinical sites outside of the ITCC consortium - Updated Medical Monitor, contact details of coordinating investigator and description of investigational product - Added additional detail regarding collection of peripheral blood and bone marrow aspirate samples - Updated protocol language and removed typographical errors
Amendment 11 June 12, 2012	- Clarify the objective of estimated CCyR rate to dasatinib therapy in children and adolescents with newly diagnosed CP-CML who are treatment naïve - Modify the definition of complete and major molecular response - Define disease free survival for each cohort - Addition of exploratory objective and endpoints for growth and development and bone mineral content
Amendment 13 December 13, 2012	- Expand Cohort 3 to include a sub-cohort of 30 pediatric subjects <18 years of age with treatment naïve CP CML who will receive dasatinib PFOS - This increase in subject number will change the plan to treat at least 50 subjects with newly diagnosed CP-CML to 80 subjects in Cohort 3.
Amendment 15 July 18, 2013	- To permanently close Cohort 2 to further enrollment
Amendment 17 October 24, 2013	- To correct the criteria for women of childbearing potential and remove information on post-menopausal women.

Amendment 18 April 13, 2016	- To add testing for HBV - Update recommendations for methods of contraception

Source: FDA Clinical Reviewer, Adapted from Study CA180226 CSR

Results

Demographics

A total of 130 subjects were treated on this study. Of these, 118 were included in the Mutation Data Set and 32 were included in the PK Data Set. The mean age of the entire study population was 12 years. Of the treated subjects, 50.8% were male, 49.2% were female and 68.5% were white. The baseline demographic characteristics for subjects with Ph+ CP-CML resistant to or intolerant of imatinib (Cohort 1) and with newly diagnosed Ph+ CP-CML (Cohort 3) are provided in the table below.

Table 18. Study CA180226 Cohorts 1 and 3 (CP-CML) - Baseline Demographics

	Cohort 3a (N=51)	Cohort 3b (N=33)	Total Newly Diagnosed (N=84)	Cohort 1 R/I CP-CML (N=29)
Age (years)				
Median	12.87	11.7	12.33	13.77
Range	1.9 – 17.8	1.8 – 17.5	1.8 – 17.8	1.4 – 20.1
Age Group (years), n (%)				
<2	1 (2.0)	1 (3.0)	2 (2.4)	1 (3.4)
≥ 2 to <7	5 (9.8)	5 (15.2)	10 (11.9)	3 (10.3)
≥ 7 to <12	16 (31.4)	12 (36.4)	28 (33.3)	6 (20.7)
≥ 12 to <18	29 (56.9)	15 (45.5)	44 (52.4)	17 (58.6)
≥ 18	0	0	0	2 (6.9)
Gender, n (%)				
Male	26 (51.0)	19 (57.6)	45 (53.6)	13 (44.8)
Female	25 (49.0)	14 (42.4)	39 (46.4)	16 (55.2)
Race, n (%)				
White	31 (60.8)	25 (75.8)	56 (66.7)	20 (69.0)
Asian	16 (31.4)	7 (21.2)	23 (27.4)	6 (20.7)
Black/African American	3 (5.9)	1 (3.0)	4 (4.8)	2 (6.9)
American Indian or Alaska Native	1 (2.0)	0	1 (1.2)	0
Other	0	0	0	1 (3.4)

Source: FDA Clinical Reviewer, Adapted from Study CA180226 CSR

An overview of the baseline disease characteristics for subjects with Ph+ CP CML resistant to or intolerant of imatinib (Cohort 1) and with newly diagnosed Ph+ CP-CML (Cohort 3) are provided in the table below.

Table 19. Study CA180226 Cohorts 1 and 3 (CP-CML) - Baseline Disease Characteristics

	Newly Diagnosed Ph+ CP-CML (n=84)			Cohort 1 R/I CP-CML (N=29)
	Cohort 3a (N=51)	Cohort 3b (N=33)	Total (N=84)	
Extramedullary Involvement, n(%)				
No	22 (43.1)	15 (45.5)	37 (44.0)	25 (86.2)
Yes	29 (56.9)	18 (54.5)	47 (56.0)	4 (13.8)
Site(s) of Extramedullary Involvement				
Lymph Node	0	0	0	0
Spleen	17 (33.3)	12 (36.4)	29 (34.5)	1 (3.4)
Liver	1 (2.0)	0	1 (1.2)	0
CNS	0	0	0	0
Spleen, Liver	11 (21.6)	6 (18.2)	17 (20.2)	3 (10.3)
Prior Therapy n(%)				
Interferon	1 (2.0)	0	1 (1.2)	4 (13.8)
Hydroxyurea	21 (41.1)	10 (30.0)	31 (36.9)	14 (48.3)
Cytarabine	0	0	0	3 (10.3)
HSCT	0	0	0	1 (3.4)
Blasts (%) in PB				
N	26	18	44	4
Mean	3	3	3	3
SD	2.8	4.5	3.5	2.2
Blasts (%) in BM				
N	44	29	73	25
Mean	3	6	4	2
SD	2.2	17.3	11.1	2.6

Source: FDA Clinical Reviewer, adapted from Study CA180226 CSR

Subject Disposition

Of the 145 subjects who were enrolled, 130 received treatment with dasatinib.

- Cohort 1 (R/I CP-CML): 29
- Cohort 2 (Advanced CML and Ph+ ALL): 17
  - BP-CML: 8
  - Ph+ ALL: 9
- Cohort 3: (Treatment naïve CP-CML): 84
  - Cohort 3a (Tablet formulation): 51
  - Cohort 3b (PFOS): 33

The median duration of dasatinib therapy in each cohort was as follows:

- Cohort 1: 49.91 months
- Cohort 2: 3.22 months
- Cohort 3: 42.30 months
  - Cohort 3a: 52.24 months
  - Cohort 3b: 27.40 months

An overview of the subject disposition for subjects in Cohorts 1 and 3 (relevant patient population) is provided in the table below.

Table 20. Study CA180226 Cohorts 1 and 3 - Subject Disposition

	Cohort 3a (N=51)	Cohort 3b (N=33)	Total Newly Diagnosed (N=84)	Cohort 1 R/I CP-CML (N=29)
On Treatment (%)	37 (72.5)	24 (72.7)	61 (72.6)	14 (48.3)
Off Treatment (%)	14 (27.5)	9 (27.3)	23 (27.4)	15 (51.7)
Reason for Discontinuation				
Progressive disease	5 (9.8)	1 (3.0)	6 (7.1)	5 (17.2)
Study drug toxicity	0	1 (3.0)	1 (1.2)	0
Death	0	0	0	0
Withdrawal by subject	2 (3.9)	1 (3.0)	3 (3.6)	3 (10.3)
Maximum clinical benefit	1 (2.0)	1 (3.0)	1 (1.2)	3 (10.3)
Non-compliance	0	0	0	1 (3.4)
Proceeded to HSCT	2 (3.9)	2 (6.1)	4 (4.8)	2 (6.9)
Loss of Response	3 (5.9)	0	3 (3.6)	0
Other*	1 (2.0)	3 (9.1)	4 (4.8)	1 (3.4)
Entered Follow-Up	14 (27.5)	9 (27.3)	23 (27.4)	14 (48.3)
Reason for End of Follow-Up				
Death	0	0	0	1 (3.4)
Withdrawal by subject	4 (7.8)	0	4 (4.8)	1 (3.4)
Lost to follow-up	0	0	0	1 (3.4)
Other	0	0	0	2 (6.9)

* Other reasons provided include: moved away and unwilling to travel (n=1), found to have T315I mutation (n=1), transitioned to adult care (n=2), second malignancy (n=1).
Source: FDA Clinical Reviewer

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The Applicant is submitting an efficacy supplement to NDA 21986 (Supplement-020) for dasatinib for use in pediatric patients with Ph+ CP-CML.

The Applicant is requesting full approval of Sprycel® tablets for the treatment of Ph+ CP-CML in pediatric patients. The request is based on two clinical studies conducted in pediatric patients between the ages of 1 year to < 18 years of age as described in the application. The sNDA proposes to update the currently approved SPRYCEL US Prescribing Information (USPI) to include labeling that supports the use of SPRYCEL tablets in pediatric populations with CP-CML.

6.1.1 Methods

Study Design

Findings from the Phase 1 Study CA180018 and the Phase 2 Study CA180226 present the effectiveness of dasatinib tablets in the pediatric CP-CML population. The data from the two studies support the efficacy of dasatinib tablets in imatinib-resistant/intolerant pediatric CP-CML patients and newly diagnosed treatment-naïve patients.

The primary efficacy endpoints for the tablet formulation in Studies CA180018 and CA180226 were Major Cytogenetic Response (MCyR), Complete Cytogenetic Response (CCyR), and Major Molecular Response (MMR). Key secondary efficacy objectives were Duration of MCyR, CCyR, and MMR and time to MCyR, CCyR, and MMR.

Cytogenetic response criteria were based on percentage of Ph+ metaphases of ≥ 20 analyzed metaphases in bone marrow aspirate, as follows:

- **Complete Cytogenetic Response (CCyR)**: 0%
- Partial Cytogenetic Response (PCyR): 1-35%
- Minor Cytogenetic Response: 36-65%
- Minimal Cytogenetic Response: 66-95%
- No Cytogenetic Response: >95%

Major Cytogenetic Response (MCyR) was defined as Complete or Partial Cytogenetic Response.

Molecular response was assessed using BCR-ABL transcript level measurement in the bone marrow or whole blood by real-time quantitative polymerase chain reaction assay (RT-qPCR). The assay was performed in a centralized lab (b) (4) Assessment of molecular response depends on subjects having the p190 or the p210 BCR-ABL transcript variant.

Major Molecular Response (MMR) for subjects with the p210 BCR-ABL transcript variant is defined according to the recommendations of Hughes et al.[4] as a ratio BCR-ABL/ABL ≤ 10^{-3} (or 0.1%) on the international scale. For a subject with the p190 BCR-ABL transcript variant, on-study assessments were compared to the subject's individual baseline BCR-ABL/ABL ratio and a reduction to < 0.1% or a 3-log reduction from baseline was considered an MMR.

In Study CA180018, the proportion of subjects in Stratum 1 with CCyR and PCyR was determined after 6 and 12 weeks of treatment and then every 12 weeks. The best cytogenetic response at any time during the study and proportion of subjects achieving Complete Hematologic Response (CHR) were also determined. Responses were also analyzed by dose level. The key efficacy endpoint for Stratum 1 was the proportion of all treated subjects with major cytogenetic response (MCyR) after 12 and 24 weeks of treatment (i.e. at start of Course 5 & 9 = Weeks 13 & 25).

In Study CA180226, cumulative response rates by month were computed for months 3, 6, 9, 12, 15, 18, 21, and 24. A subject was a defined as a responder if the response occurred at any time on study, i.e. the response needed to occur on treatment but may be later than month 24.

Sample Size
For Study CA180018, the sample size was not based on statistical power to detect a specific response rate but on the feasibility of accrual and on the dose levels that were used for the escalations of the starting dose. In Stratum 1 (CP-CML), at least 12 subjects in each stratum were treated to meet the primary objective (6 subjects at the 60 mg/m^2 starting dose; and 6 subjects at the 80 mg/m^2 starting dose, unless there was excessive toxicity at either dose, or no clinical need to escalate to 80 mg/m^2). Up to additional 4 patients were treated at the 60 mg/m^2 dose level in Stratum 1 to expand the number of patients at the dose level that was selected for the planned phase 2 study.

Dose escalation was based on the tolerability at a given dose level and the clinical efficacy at a given dose. The recommended Phase 2 dose was determined based on the aggregation of safety data for the study strata, and an assessment of safety at a minimum of 2 dose levels was planned. Therefore, approximately 56 subjects (up to 16 in each of stratum 1 (CP-CML) and 2/3 (Ph+ ALL or AP/BP-CML) and up to 24 in stratum 4 (Ph-ALL/AML) were planned to be treated in Study CA180018.

For Cohort 1 (CP-CML) in Study CA180226, a response rate in excess of 30% for MCyR was considered of clinical interest. The study tested the null hypothesis that the true MCyR rate is less than or equal to 30% versus the alternative hypothesis that it exceeds 30%. Based on a one-sided type I error rate of 2.5% assuming a 60% true MCyR rate (30 % more than the response rate under the null hypothesis), 25 response-evaluable subjects are required, to have at least 84% power to reject the null hypothesis.

For Cohort 3A in Study CA180226, a response rate in excess of 55% for CCyR was considered of clinical interest. The study tested the null hypothesis that the true CCyR rate is less than or equal to 55% versus the alternative hypothesis that it exceeds 55%. Assuming a one-sided type I error rate of 2.5% and assuming a 75% true CCyR rate among newly diagnosed patients with CP CML (20% more than the response rate under the null hypothesis), 50 response-evaluable subjects in Cohort 3A are required, to have at least 83% power to reject the null hypothesis.

Efficacy Analysis
Cumulative Response rates (MCyR, CCyr and MMR) were estimated by Cohort (imatinib resistant/intolerant patients and newly diagnosed treatment naïve patients) and by time (at 3, 6, 12, and 24 months) on the ITT population and respective 95% two-sided exact confidence intervals were computed based on Clopper-Pearson.

Median time to responses for MCyR, CCyR and MMR and respective median duration of responses were estimated based on Kaplan-Meier (K-M) analysis. Respective two-sided 95% confidence intervals for the median of duration of response were computed based on the Brookmeyer and Crowley log-log transformation.

6.1.2 Demographics

The table below presents the patient characteristics for the imatinib resistant/intolerant patients in Studies CA180018 and CA180226. The majority of subjects were White and between 12 and 17 years of age from Europe.

Table 21. Patient Demographics: Imatinib-resistant/intolerant CP-CML

	Subjects with Imatinib-resistant/intolerant CP-CML	
	CA180018 Stratum 1 N=17	CA180226 Cohort 1 N=29
Age (years)		
Mean (SD)	12.4 (4.1)	12.60 (4.774)
Median (min-max)	13.0 (4.0-17.0)	13.77 (1.4-20.1)
Age Category (no., %)		
< 2	0	1 (3.4)
≥ 2 to < 7	2 (11.8)	3 (10.3)
≥ 7 to < 12	6 (35.3)	6 (20.7)
≥ 12 to < 18	9 (52.9)	17 (58.6)
≥ 18	0	2 (6.9)
Sex (no., %)		
Male	11 (64.7)	13 (44.8)
Female	6 (35.3)	16 (55.2)
Race (no., %)		
White	16 (94.1)	20 (69.0)
Black or African American	0	2 (6.9)
Asian	1 (5.9)	6 (20.7)
American Indian or Alaska native	0	0
Other	0	1 (3.4)
Ethnicity (no., %)		
Hispanic or Latino	0	2 (6.9)
Not Hispanic or Latino	0	4 (13.8)
Not Reported	17 (100.0)	23 (79.3)
Geographic region (no., %)		
North America	0	4
Europe	17	11
Asia	0	6
Rest of world	0	8

Source: CA180018 CSR Table 5.3.1, and CA180226 CSR Table S.3.1.

Note: Age is based on the date of informed consent. Data are as of the primary database lock dates for each study.

Statistical Reviewer Comment: The frequency counts for geographic region for CA180226 Cohort 1 in the analytic dataset differed from the counts reported in the CSR. The CSR reported the following frequency counts: North America 5, Europe 10, Asia 7, and Rest of the World 7.

The table below presents the patient characteristics for the newly diagnosed treatment-naïve CP-CML. The majority of subjects were White/non-Latino and between 12 and 17 years of age.

Table 22. Patient Demographics: Newly Diagnosed Treatment-Naive CP-CML

	Cohort 3a (tablet dosing) N=51
Age (years)	
Mean (SD)	12.28 (4.084)
Median (min-max)	12.87 (1.9, 17.8)
Age Category (no., %)	
< 2	1 (2.0)
≥ 2 to < 7	5 (9.8)
≥ 7 to < 12	16 (31.4)
≥ 12 to < 18	29 (56.9)
Sex (no., %)	
Male	26 (51.0)
Female	25 (49.0)
Race (no., %)	
White	31 (60.8)
Black or African American	3 (5.9)
Asian	16 (31.4)
American Indian or Alaska native	1 (2.0)
Other	0
Ethnicity (no., %)	
Hispanic or Latino	1 (2.0)
Not Hispanic or Latino	13 (25.5)
Not Latino	37 (72.5)

Source: CA180226 Final CSR Table S.3.1.

6.1.3 Subject Disposition

See Section 5.3.

6.1.4 Analysis of Primary Endpoint(s)

All primary efficacy results were based on the ITT population. Table 23 presents the cumulative major cytogenetic response rate and respective 95% confidence intervals at 3, 6, 12, and 24 months for the newly diagnosed treatment naïve and imatinib resistant/intolerant patient populations. The cumulative major cytogenetic response rate

at 24 months for was 98% (95% CI: 89.6%-100%) for the newly diagnosed treatment naïve patients in Study CA180226 and 89.10% (95% CI: 76.4%-96.4%) for the imatinib resistant/intolerant patients in Study CA180018.

Table 24 presents the cumulative major cytogenetic response rate and respective 95% confidence intervals at 3, 6, 12, and 24 months for the newly diagnosed treatment naïve and imatinib resistant/intolerant patient populations. The cumulative complete cytogenetic response rate at 24 months was 96.1% (95% CI: 86.5%-99.5%) for the newly diagnosed treatment naïve patients in Study CA180226, and 82.6% (95% CI: 68.6%-92.2%) for the imatinib resistant/intolerant patients in Study CA180018.

Table 25 presents the cumulative major molecular response rate and respective 95% confidence intervals at 3, 6, 12, and 24 months for the newly diagnosed treatment naïve and imatinib resistant/intolerant patient populations. The cumulative major molecular response rate at 24 months for was 74.5% (95% CI: 60.4%-85.7%) for the newly diagnosed treatment naïve patients in Study CA180226 and 52.2% (95% CI: 36.9%-67.1%) for the imatinib resistant/intolerant patients in Study CA180018.

Table 23. Major Cytogenetic Response by Time

	3 months	6 months	12 months	24 months
MCyR (95% CI)				
Newly Diagnosed (Cohort 3A Tablet) (N=51)	60.80% (46.1%-74.2%)	90.20% (78.6%-96.7%)	98.00% (89.6%-100.0%)	98.00% (89.6%-100.0%)
Prior Imatinib (Pooled Stratum 1 / Cohort 1) (n=46)	60.90% (45.4%-74.9%)	82.60% (68.6%-92.2%)	89.10% (76.4%-96.4%)	89.10% (76.4%-96.4%)

Source: FDA Statistical Reviewer

Table 24. Complete Cytogenetic Response by Time

	3 months	6 months	12 months	24 months
CCyR (95% CI)				
Newly Diagnosed (Cohort 3A Tablet) (N=51)	43.10% (29.3%-57.8%)	66.70% (52.1%-79.2%)	96.10% (86.5%-99.5%)	96.10% (86.5%-99.5%)
Prior Imatinib (Pooled Stratum 1 / Cohort 1) (n=46)	45.70% (30.9%-61.0%)	71.70% (56.5%-84.0%)	78.30% (63.6%-89.1%)	82.60% (68.6%-92.2%)

Source: FDA Statistical Reviewer

Table 25. Major Molecular Response by Time

MMR (95% CI)	3 months	6 months	12 months	24 months
Newly Diagnosed (Cohort 3A Tablet) (N=51)	7.80% (2.2%-18.9%)	31.40% (19.1%-45.9%)	56.90% (42.2%-70.7%)	74.50% (60.4%-85.7%)
Prior Imatinib (Pooled Stratum 1 / Cohort 1) (n=46)	15.20% (6.3%-28.9%)	26.10% (14.3%-41.1%)	39.10% (25.1%-54.6%)	52.20% (36.9%-67.1%)

Source: FDA Statistical Reviewer

Table 26 below presents the overall response rates for the pooled imatinib-resistant resistant/intolerant CP-CML patients in Studies CA180018 and CA180226 (Stratum 1 and Cohort 1) and the newly diagnosed treatment naïve CP-CML patients in Study CA180226 (Cohort 3a), all taking the tablet formulation of dasatinib. The overall MCyR, CCyR, MMR rates for the imatinib resistant/intolerant CP-CML patients were 89.1%, 82.6%, and 56.5%, respectively. The overall MCyR, CCyR, MMR rates for the newly diagnosed treatment naive CP-CML patients were 98%, 96.1%, and 88.2%, respectively.

Table 26. Results for Overall Response Rate

	Imatinib-resistant or intolerant Ph+ CP-CML			Cohort 3: Newly Dx Treatment Naïve Ph+ CP-CML
	Stratum 1 60 and 80 mg/m2 tablet (N=17)	Cohort 1 60 mg/m2 tablet (N=29)	Total (N=46)	Cohort 3A 60 mg/m2 Tablet (N=51)
MCyR Overall	15 (88.2% (64%, 98%)) *	26 (89.8% (72.6%, 97.8%))	**41 (89.1% (76.4%, 96.3%))**	**50 (98% (89.6%, 99.9%))**
CCyR Overall	14 (82.4% (57%, 96.2%))	24 (82.8% (64.2%, 94.2%))	**38 (82.6% (68.6%, 92.2%))**	**49 (96.1% (86.5%, 99.5%))**
MMR Overall	8 (47.1% (23%, 72.1%))	18 (62.1% (42.2%, 79.3%))	**26 (56.5% (41.1%, 71.1%))**	**45 (88.2% (76.1%, 95.6%))**

***Count (Response Rate (95% Confidence Interval))**

Source: FDA Statistical Reviewer

6.1.5 Analysis of Secondary Endpoints(s)

The median duration of MCyR, CCyR and MMR were not reached in the pooled imatinib resistant/intolerant CP-CML patients and the newly diagnosed treatment naïve CP-CML patients.

The median time to response for MCyR was 2.86 months (95% CI: 2.76 months, 3.45 months) in the pooled imatinib resistant/intolerant CP-CML patients. The median time to response for CCyR was 3.22 months (95% CI: 2.76 months, 4.63 months) in the

pooled imatinib resistant/intolerant CP-CML patients. The median time to response for MMR was 8.28 months (95% CI: 4.99 months, 11.76 months) in the pooled imatinib resistant/intolerant CP-CML patients.

The median time to response for MCyR was 2.92 months (95% CI: 2.76 months, 4.30 months) in the newly diagnosed treatment naïve CP-CML patients. The median time to response for CCyR was 5.52 months (95% CI: 2.99 months, 6.14 months) in the newly diagnosed treatment naïve CP-CML patients. The median time to response for MMR was 8.84 months (95% CI: 6.14 months, 11.66 months) in the newly diagnosed treatment naïve CP-CML patients.

6.1.6 Other Endpoints

Not applicable for this review.

6.1.7 Subpopulations

The Table below summarizes the MCyR, CCyR, and MMR rates and exact 95% confidence intervals by age, gender, race, and geographical region subgroups for the imatinib resistant/intolerant patients in Studies CA180018 and CA180226.

Table 27. Subgroup Analyses for Pediatric Patients with CP-CML who are Imatinib Resistant/Intolerant

	Subjects in category	MCyR Rate		CCyR Rate		MMR Rate	
		Subjects (%)	95% CI	Subjects (%)	95% CI	Subjects (%)	95% CI
Age category (no., %)							
< 2 years	1	1 (100.0)	2.5-100.0	1 (100.0)	2.5-100.0	0 (0)	0-97.5
≥ 2 to < 7 years	5	4 (80.0)	28.4-99.5	4 (80.0)	28.4-99.5	1 (20.0)	0.5-71.6
≥ 7 to < 12 years	12	11 (91.7)	61.5-99.8	11 (91.7)	61.5-99.8	7 (58.3)	27.7-84.8
≥ 12 to < 18 years	26	23 (88.5)	69.8-97.6	20 (76.9)	56.4-91.0	16 (61.5)	40.6-79.8
≥ 18 years	2	2 (100.0)	15.8-100.0	2 (100.0)	15.8-100.0	2 (100.0)	15.8-100
Sex (no., %)							
Male	24	22 (91.7)	73.0-99.0	20 (83.3)	62.6-95.3	15 (62.5)	40.6-81.2
Female	22	19 (86.4)	65.1-97.1	18 (81.8)	59.7-94.8	11 (50.0)	28.2-71.8
Race category (no., %)							
White	36	32 (88.9)	73.9-96.9	30 (83.3)	67.2-93.6	20 (55.6)	38.1-72.1
Asian	7	7 (100.0)	59.0-100.0	7 (100.0)	59.0-100.0	5 (71.4)	29.0-96.3
Black or African American	2	1 (50.0)	1.3-98.7	1 (50.0)	1.3-98.7	1 (50.0)	1.3-98.7
Other	1	1 (100.0)	2.5-100.0	0	0.0-97.5	0 (0)	0-97.5
Geographical region (no., %)							
Europe	28	24 (85.7)	67.3-96.0	21 (75.0)	55.1-89.3	13 (46.4)	27.5-66.1
North America	4	3 (75.0)	19.4-99.4	3 (75.0)	19.4-99.4	3 (75.0)	19.4-99.4
Asia	6	6 (100.0)	54.1-100.0	6 (100.0)	54.1-100.0	5 (83.3)	35.9-99.6
Rest of world	8	8 (100.0)	63.1-100.0	8 (100.0)	63.1-100.0	5 (62.5)	24.5-91.5

Source: FDA Statistical Reviewer

The Table below summarizes the MCyR, CCyR, and MMR rates and exact 95% confidence intervals by age, gender, race, and geographical region subgroups for the newly diagnosed treatment naïve patients in Study CA180226.

Table 28. Subgroup Analyses for Pediatric Patients with Treatment-Naive CP-CML

	Subjects in category	MCyR Rate		CCyR Rate		MMR Rate	
		Subjects (%)	95% CI	Subjects (%)	95% CI	Subjects (%)	95% CI
Age category (no., %)							
< 2 years	1	1 (100.0)	2.5-100.0	1 (100.0)	2.5-100.0	1 (100.0)	2.5-100.0
≥ 2 to < 7 years	5	5 (100.0)	47.8-100.0	5 (100.0)	47.8-100.0	4 (80.0)	28.4-99.5
≥ 7 to < 12 years	16	16 (100.0)	79.4-100.0	16 (100.0)	79.4-100.0	16 (100.0)	79.4-100.0
≥ 12 to < 18 years	29	28 (96.6)	82.2-99.9	27 (93.1)	77.2-99.2	24 (82.8)	64.2-94.2
Sex (no., %)							
Male	26	26 (100.0)	86.8-100.0	26 (100.0)	86.8-100.0	22 (84.6)	65.1-95.6
Female	25	24 (96.0)	79.6-99.9	23 (92.0)	74.0-99.0	23 (92.0)	74.0-99.0
Race category (no., %)							
White	31	31 (100.0)	88.8-100.0	30 (96.8)	83.3-99.9	28 (90.3)	74.2-98.0
Asian	16	16 (100.0)	86.8-100.0	16 (100.0)	86.8-100.0	15 (93.8)	69.8-99.8
Black or African American	3	2 (66.7)	9.4-99.2	2 (66.7)	9.4-99.2	1 (33.3)	0.8-90.6
Other	1	1 (100.0)	2.5-100.0	1 (100.0)	2.5-100.0	1 (100.0)	2.5-100.0
Geographical region (no., %)							
Europe	7	7 (100.0)	59.0-100.0	7 (100.0)	59.0-100.0	6 (85.7)	42.1-99.6
North America	20	20 (100.0)	83.2-100.0	19 (95.0)	75.1-99.9	18 (90.0)	68.3-98.8
Asia	14	14 (100.0)	76.8-100.0	14 (100.0)	76.8-100.0	13 (92.9)	66.1-99.8
Rest of world	10	9 (90.0)	55.5-99.7	9 (90.0)	55.5-99.7	8 (80.0)	44.4-97.5

Source: FDA Statistical Reviewer

Statistical Reviewer Comment: The subgroup analyses were exploratory and no adjustments for multiple comparisons were considered. Subgroup frequencies were small for many age and race categories and results should be interpreted with caution.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Study CA180018 pooled two different doses, 60 mg/m^2 and 80 mg/m^2, in the imatinib resistant/intolerant patients in Stratum 1. The Applicant's reasoning for pooling doses in the analysis, conveyed during the July 7, 2017 Application Orientation Meeting, was that the response rates were similar across the two doses across time. An analysis stratified on doses for Stratum 1 in Study CA180018 was conducted and results are presented in the Table below.

Table 29. Response Rates by Dosage Analysis

	3 months	6 months	12 months	24 months
MCyR (95% CI)				
Prior Imatinib (Stratum 1) n=17	70.60% (44.0%-89.7%)	88.20% (63.6%-98.5%)	88.20% (63.6%-98.5%)	88.20% (63.6%-98.5%)
60 mg/m2 n=11	72.70% (39.0%-94.0%)	81.80% (48.2%-97.7%)	81.80% (48.2%-97.7%)	81.80% (48.2%-97.7%)
80 mg/m2 n=6	66.70% (22.3%-95.7%)	100% (54.1%-100%)	100% (54.1%-100%)	100% (54.1%-100%)
Cohort 1: 60 mg/m2 n=29	55.20% (35.7%-73.6%)	79.30% (60.3%-92.0%)	89.70% (72.6%-97.8%)	89.70% (72.6%-97.8%)
χ2 test (2 df) p-value	0.57	0.475	0.508	0.508
Stratum 1/Cohort 1: 60 mg/m2 n=40	60% (43.3%-75.1%)	80% (64.4%-90.9%)	87.5% (73.2%-95.8%)	87.5% (73.2%-95.8%)
CCyR (95% CI)				
Prior Imatinib (Stratum 1) n=17	52.90% (27.8%-77.0%)	82.40% (56.6%-96.2%)	82.40% (56.6%-96.2%)	82.40% (56.6%-96.2%)
60 mg/m2 n=11	45.50% (16.7%-76.6%)	72.70% (39.0%-94.0%)	72.70% (39.0%-94.0%)	72.70% (39.0%-94.0%)
80 mg/m2 n=6	66.70% (22.3%-95.7%)	100% (54.1%-100%)	100% (54.1%-100%)	100% (54.1%-100%)
Cohort 1: 60 mg/m2 n=29	41.40% (23.5%-61.1%)	65.50% (45.7%-82.1%)	75.90% (56.5%-89.7%)	82.80% (64.2%-94.2%)
χ2 test (2 df) p-value	0.527	0.232	0.375	0.365
Stratum 1/Cohort 1: 60 mg/m2 n=40	42.50% (27.0%-59.1%)	67.50% (50.9%-81.4%)	75.00% (58.8%-87.3%)	80.00% (64.4%-90.9%)
MMR (95% CI)				
Prior Imatinib (Stratum 1) n=17	11.80% (1.5%-36.4%)	17.60% (3.8%-43.4%)	35.30% (14.2%-61.7%)	47.10% (23.0%-72.2%)
60 mg/m2 n=11	18.20% (2.3%-51.8%)	18.20% (2.3%-51.8%)	36.40% (10.9%-69.2%)	54.50% (23.4%-83.3%)
80 mg/m2 n=6	0.00% (0.0%-45.9%)	16.70% (0.4%-64.1%)	33.30% (4.3%-77.7%)	33.30% (4.3%-77.7%)
Cohort 1: 60 mg/m2 n=29	17.20% (5.8%-35.8%)	31% (15.3%-50.8%)	41.40% (23.5%-61.1%)	55.20% (35.7%-73.6%)
χ2 test (2 df) p-value	0.537	0.609	0.913	0.611
Stratum 1/Cohort 1: 60 mg/m2 n=40	17.5% (7.3%-32.8%)	27.5% (14.6%-43.9%)	40% (24.9%-56.7%)	55% (38.5%-70.7%)

Source: FDA Statistical Reviewer

Statistical Reviewer Comment: Chi-square (χ2) tests of differences in proportions were conducted comparing response rates between dose categories (Stratum 1) in Study CA180018 and response rates (MCyR, CCyR, and MMR) in Cohort 1 of Study CA180226. There were no statistically significant differences in the response rates across the groups at each time-point. However, no conclusion can be made about the difference, due to the small cell frequencies and limitation of cross study comparison.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not Applicable.

6.1.10 Additional Efficacy Issues/Analyses

Not Applicable.

Labeling recommendation:

Study CA180018 was a single-arm trial that pooled two different doses, 60 mg/m^2 and 80 mg/m^2, in the imatinib resistant/intolerant patients in Stratum 1. Furthermore, the patients in Stratum 1 were pooled with imatinib resistant/intolerant patients in Cohort 1 of Study CA180226. Although, the chi-square tests of differences in proportions reported in Table 29 were not statistically significant across time, a clinical reason for pooling different doses should be provided.

The overall response rates of MCyR, CCyR, and MMR in imatinib resistant/intolerant subjects and newly diagnosed treatment naïve subjects exceeded the clinically relevant thresholds specified in the power calculations in Section 6.1.1.

Table 26 presents the overall response rates for the pooled imatinib-resistant resistant/intolerant CP-CML patients in Studies CA180018 and CA180226 (Stratum 1 and Cohort 1) and the newly diagnosed treatment naïve CP-CML patients in Study CA180226 (Cohort 3A), all taking the tablet formulation of dasatinib. The overall MCyR, CCyR, MMR rates for the imatinib resistant/intolerant CP-CML patients were 89.1%, 82.6%, and 56.5%, respectively. The overall MCyR, CCyR, MMR rates for the newly diagnosed treatment naive CP-CML patients were 98%, 96.1%, and 88.2%, respectively. Table 26 further shows increasing trends for cumulative response rates for CCyR, MCyR, and MMR across time, from 3 months to 24 months.

The median duration of MCyR, CCyR and MMR were not reached in the pooled imatinib resistant/intolerant CP-CML patients. The median duration of MCyR, CCyR and MMR were not reached in the newly diagnosed treatment naïve CP-CML patients.

The median time to response for MCyR was 2.86 months (95% CI: 2.76 months, 3.45 months) in the pooled imatinib resistant/intolerant CP-CML patients. The median time

to response for CCyR was 3.22 months (95% CI: 2.76 months, 4.63 months) in the pooled imatinib resistant/intolerant CP-CML patients. The median time to response for MMR was 8.28 months (95% CI: 4.99 months, 11.76 months) in the pooled imatinib resistant/intolerant CP-CML patients.

The median time to response for MCyR was 2.92 months (95% CI: 2.76 months, 4.30 months) in the newly diagnosed treatment naïve CP-CML patients. The median time to response for CCyR was 5.52 months (95% CI: 2.99 months, 6.14 months) in the newly diagnosed treatment naïve CP-CML patients. The median time to response for MMR was 8.84 months (95% CI: 6.14 months, 11.66 months) in the newly diagnosed treatment naïve CP-CML patients.

The results from the pooled imatinib resistant/intolerant patients Studies CA180018 and CA180226 and the newly diagnosed treatment naïve patients on tablet formulation in Study CA180226 demonstrated high response rates for MCyR, CCyR, and MMR. Increasing trends in cumulative response rates across time were also demonstrated in both cohorts of subjects. Whether the data and the analyses from the current submission demonstrate an overall favorable benefit vs. risk profile is deferred to the clinical team review of the application.

The overall response rates for Major Cytogenetic Response (MCyR), Complete Cytogenetic Response (CCyR), and Major Molecular Response (MMR) may be included in the label along with cumulative response rate at 3, 6, 12, and 24 months. Duration of MCyR, CCyR, and MMR should be provided as data becomes more mature. Time to response for MCyR, CCyR, and MMR would be acceptable for inclusion in the label.

Clinical Reviewer Comment: The overall efficacy findings were favorable and support the proposed indication.

7 Review of Safety

Safety Summary

A detailed analysis of safety outcomes was conducted using data from Studies CA180018 and CA180226. Within these studies, only data from subjects with Ph+ CP-CML, including those with newly diagnosed treatment naïve disease as well as those who were refractory to or intolerant of imatinib therapy, were analyzed. Due to the differences in underlying disease characteristics and varying dosages of dasatinib used in these studies based on the underlying diagnosis, subjects with Ph+ ALL, AP-CML, BP-CML, Ph- ALL, Ph- AML were excluded from the safety analyses for this application. The total patient population analyzed included 130 subjects with Ph+ CP-CML across the two studies. Of these, 84 had newly diagnosed treatment naïve CP-CML and 46 were resistant to or intolerant of prior therapy with imatinib.

Overall, the safety profile of dasatinib in pediatric patients is similar to, or better than, that in adults. There were no unexpected safety findings and the majority of adverse events were consistent with the known safety profile of dasatinib. The most common treatment-emergent adverse evets in pediatric subjects with CP-CML were abdominal pain, diarrhea, headache, vomiting and pyrexia. There were four deaths in the pooled patient population, all of which occurred in subjects who were previously treated and resistant to or intolerant of imatinib. There were no deaths in the treatment naïve patient population. The four deaths all occurred after treatment completion and there were no deaths during treatment or within 30 days of the last treatment dose of dasatinib.

7.1 Methods

The safety review for dasatinib in pediatric subjects with Ph+ CP-CML included the review of the following items submitted by the Applicant.

- Clinical study reports and statistical analysis plans for Studies CA180018 and CA180226
- Raw and derived datasets for Studies CA180018 and CA180226
- Clinical study report and data from supportive study CA180038
- Response to information requests
- Case report forms and narratives for studies
- Proposed labeling for dasatinib

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety summary focuses on safety data from:

1. Study CA180018: A phase 1, open-label, dose escalation study in pediatric patients with relapsed/refractory leukemias.

2. Study CA180226: A phase 2, open-label, non-randomized, multi-center single arm study in pediatric patients with newly diagnosed Ph+ CP CML or with Ph+ leukemias resistant or intolerant to imatinib.

7.1.2 Categorization of Adverse Events

The severity of adverse events was graded by the investigators according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0. The causal relationship to investigational product (certain, probably, possibly, not likely, not related) was determined by the study investigator.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) according to the most recent version of the dictionary at the time of the analysis (version 19.0).

Safety presentations of AEs, SAEs, AEs leading to discontinuation, and laboratory abnormalities are based on all treated subjects using a safety window of 30 days after last dose.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

For the purpose of this application, the Applicant has pooled data from the subjects with Ph+ CP-CML in Study CA180018 (n=17) and subjects with Ph+ CP-CML in Study CA180226 (n=113).

7.2 Adequacy of Safety Assessments

See section 3.1 for information regarding the data quality.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The pooled safety population included a total of 130 pediatric subjects with Ph+ CP CML enrolled in the two clinical studies (CA180018 and CA180226). Of these, 46 were resistant or intolerant to imatinib and 84 were newly diagnosed. The median age was 12.83 years and the majority of subjects were white (70.8%) and male (53.1%). The majority of subjects had baseline Karnofsky/Lansky Performance Status of 100.

The table below depicts the baseline demographic characteristics for the pooled safety population.

Table 30. Baseline Demographics - Pooled Safety Population

	Pediatric Patients with Ph+ CP CML Treated with Dasatinib (n=130)				
	Newly Diagnosed Ph+ CP CML (n=84)			Imatinib Resistant/ Intolerant Ph+ CP-CML (n=46)	Total CP-CML (n=130)
	Cohort 3a: Tablet (n=51)	Cohort 3b: PFOS (n=33)	Total (n=84)		
Median age, years (range)	12.87 (1.9-17.8)	11.7 (1.8-17.5)	12.33 (1.8-17.8)	13.75 (1.40-20.1)	12.83 (1.4 – 20.1)
Age, n(%)					
<2	1 (2.0)	1 (3.0)	2 (2.4)	1 (2.2)	3 (2.3)
≥ 2 to <7	5 (9.8)	5 (15.2)	10 (11.9)	5 (10.9)	15 (11.5)
≥ 7 to <12	16 (31.4)	12 (36.4)	28 (33.3)	12 (26.1)	40 (30.8)
≥ 12 to <18	29 (56.9)	15 (45.5)	44 (52.4)	26 (56.5)	70 (53.8)
≥ 18	0	0	0	2 (4.3)	2 (1.5)
Race, n (%)					
White	31 (60.8)	25 (75.8)	56 (66.7)	36 (78.3)	92 (70.8)
Asian	16 (31.4)	7 (21.2)	23 (27.4)	7 (15.2)	30 (23.1)
Black/African American	3 (5.9)	1 (3.0)	4 (4.8)	2 (4.3)	6 (4.6)
American Indian or Alaska	1 (2.0)	0	1 (1.2)	0	1 (0.8)
Native	0	0	0	1 (2.2)	1 (0.8)
Other					
Female, n(%)	25 (49.0)	14 (42.4)	39 (46.4)	22 (47.8)	61 (46.9)
Prior Treatment Status					
Naive	51 (100.0)	33 (100.0)	84 (100.0)	0	84 (64.6)
Resistant to Imatinib	0	0	0	36 (78.3)	36 (27.7)
Intolerant to Imatinib	0	0	0	10 (21.7)	10 (7.7)

Source: FDA Clinical Reviewer, Adapted from ISS.

Exposure was similar between the patients with imatinib resistance/intolerance and those who were treatment naïve. In the CP-CML pooled population, the median daily dose of study therapy was 59.81 mg/m^2/day. More patients in the imatinib resistant/intolerant arms had dose escalations and dose reductions. The majority of the subjects (53.1%) had a duration of therapy >36 months. Most newly-diagnosed subjects with CP-CML (82.1%) had at least 24 months of treatment. Subjects who received the PFOS (CA180226, Cohort 3b) had a shorter median duration of exposure (27.4 months), as enrollment in this cohort was initiated by a protocol amendment after treatment of subjects in Cohort 3 by tablet had begun.

The overall exposure for all subjects with Ph+ CML is provided in the table below.

Table 31. Exposure - Pooled Population

	Pediatric Patients with Ph+ CP CML Treated with Dasatinib (n=130)			
	Newly Diagnosed Ph+ CP CML (n=84)		Imatinib Resistant/ Intolerant Ph+ CP-CML (n=46)	Total CP-CML (n=130)
	Cohort 3a: Tablet (n=51)	Cohort 3b: PFOS (n=33)		
Average daily dose (mg/m2/day), Mean (SD)	56.9 (7.3)	71.26 (10.5)	63.29 (12.7)	60.9 (11.0)
Dose Interruptions, n(%)	31 (60.8)	13 (39.4)	26 (56.5)	70 (53.8)
Dose Reductions, n(%)	6 (11.8)	2 (6.1)	11 (23.9)	19 (14.6)
Dose Escalations, n(%)	9 (17.6)	5 (12.2)	17 (37.0)	31 (23.8)
Duration of Treatment (months), Median (range)	52.2 (7.6-75.2)	27.4 (0.1-42.0)	38.9 (1.9-99.6)	42.3 (0.1-99.6)
Subjects remaining on treatment	37 (72.5)	24 (72.7)	15 (32.6)	76 (58.5)

Source: FDA Clinical Reviewer's Analysis

Dose Modifications and Interruptions

A total of 70 (53.8%) of subjects had at least 1 dose interruption, 19 (14.6%) had at least 1 dose reduction and 31 (23.8%) had at least 1 dose escalation. Reasons for interruption, reduction or escalation are provided in the table below.

Table 32. Dasatinib Dose Modifications

	Treatment Naive N=84	Imatinib Resistant/ Intolerant N=46	Total CP-CML N=130
Subjects with at least 1 dose Interruption, n(%)	44 (52.4)	26 (56.5)	70 (53.8)
Reason for dose interruption, n(%)			
Dosing error	9 (10.7)	8 (17.4)	17 (13.1)
Hematologic toxicity	19 (22.6)	6 (13.0)	25 (19.2)
Non-hematologic toxicity	13 (15.5)	8 (17.4)	21 (16.2)
Subject missed dose	0	2 (4.3)	2 (1.5)
Other	3 (3.6)	2 (4.3)	5 (3.8)
Subjects with at least 1 dose reduction, n(%)	8 (9.5)	11 (23.9)	19 (14.6)
Reason for dose reduction, n(%)			
Dosing error	0	3 (6.5)	3 (2.3)
Hematologic toxicity	6 (7.1)	3 (6.5)	9 (6.9)
Non-hematologic toxicity	2 (2.4)	3 (6.5)	5 (3.8)
Other	0	2 (4.3)	2 (1.5)

Subjects with at least 1 dose escalation, n(%)	14 (16.7)	17 (37.0)	31 (23.8)
Reason for dose escalation, n(%)			
Persistent molecular BCR-ABL signal	0	5 (10.9)	5 (3.8)
Resistance	10 (11.9)	4 (8.7)	14 (10.8)
Stable or increasing % Ph+ metaphases	0	2 (4.3)	2 (1.5)
Other	4 (4.8)	6 (13.0)	10 (7.7)

Source: FDA Clinical Reviewer's Analysis

7.2.2 Explorations for Dose Response

See Section 6.1.8.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable to this supplement.

7.2.4 Routine Clinical Testing

Refer to Section 5.3.1 for the schedule of safety assessments.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to the Clinical Pharmacology review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Refer to Section 2.4 of this review.

7.3 Major Safety Results

In the pooled patient population almost all patients (99.2%) experienced at least one TEAE, and 84 (64.4%) experienced at least 1 Grade 3 or 4 TEAE. A summary of the major safety events is provided in the table below.

Table 33. Safety Summary for Ph+ CP-CML (Pooled Patient Population)

	Pediatric Patients with Ph+ CP CML Treated with Dasatinib (n=130)			
	Newly Diagnosed Ph+ CP CML (n=84)		Imatinib Resistant/ Intolerant Ph+ CP-CML (n=46)	Total CP-CML (n=130)
	Cohort 3a: Tablet (n=51)	Cohort 3b: PFOS (n=33)		
Subjects with ≥ 1 TEAE	51 (100.0)	33 (100.0)	45 (97.8)	129 (99.2)
Subjects with ≥ 1 Grade 3 or 4 TEAE	32 (65.7)	23 (69.7)	29 (63.0)	84 (64.4)
SAEs (Any)	19 (37.3)	9 (27.3)	21 (45.7)	49 (37.7)
Related SAEs	6 (11.8)	2 (6.1)	8 (17.1)	16 (12.3)
AE leading to discontinuation	0	1 (3.0)	1 (2.2)	2 (1.5)
Deaths	0	0	4 (8.7)	4 (3.1)
Deaths within 30 days of last dose	0	0	0	0

Source: FDA Clinical Reviewer's Analysis

7.3.1 Deaths

There were four deaths in the pooled patient population, all of which occurred in subjects who were previously treated and resistant or intolerant to imatinib. There were no deaths in the treatment naïve patient population. The four deaths all occurred after treatment completion and there were no deaths during treatment or within 30 days of the last treatment dose of dasatinib. One subject died due to disease progression. Narratives of the three subjects who died from causes other than disease progression are provided below.

1. Subject CA180018 (b) (6) (fatal bleeding)
   The patient was a (b) (6) with CP-CML who was receiving treatment with dasatinib 80 mg/m . She experienced a cerebral hemorrhage approximately 1.5 months after last dasatinib dose. The platelet levels while on study and receiving treatment were normal or Grade 1. On the last dosing day (Day 155), her platelet count was 315,000/µL.

2. Subject CA180018 (b) (6) (respiratory failure)
   This subject was a (b) (6) with CP-CML who was receiving treatment with dasatinib 80 mg/m . She died due to respiratory failure approximately 3 months after the last dasatinib dose. After completion of dasatinib therapy, (b) (6) received a HSCT.

3. Subject CA180226 (b) (6) (digestive tract bleeding)
   This subject was a 7 year old (b) (6) with CP-CML. She died approximately 1 year after completion of therapy secondary to digestive tract bleeding.

7.3.2 Nonfatal Serious Adverse Events

In the pooled patient population, SAEs were reported in 37.7% of subjects. A total of 21 subjects (45.7%) in the imatinib resistant/intolerant treatment group, and 28 (33.3%) in the treatment naïve group experienced at least one serious adverse event (SAE). The most common SAEs overall were anemia, pyrexia and gastroenteritis.

The table below depicts the non-fatal serious adverse events for the pooled patient population.

Table 34. Serious Adverse Events by Preferred Term (Pooled Population)

	Pediatric Patients with Ph+ CP CML Treated with Dasatinib (n=130)			
	Newly Diagnosed Ph+ CP CML (n=84)		Imatinib Resistant/ Intolerant Ph+ CP-CML (n=46)	Total CP-CML (n=130)
	Cohort 3a: Tablet (n=51)	Cohort 3b: PFOS (n=33)		
# of Subjects with at least 1 SAE, n(%)	**19 (37.3)**	**9 (27.3)**	**21 (45.7)**	**49 (37.7)**
Anemia	8 (15.7)	1 (3.0)	5 (10.9)	14 (10.8)
Pyrexia	2 (3.9)	3 (9.0)	3 (6.5)	8 (6.2)
Gastroenteritis	3 (5.9)	1 (3.0)	2 (4.3)	6 (4.6)
Diarrhea	0	3 (9.0)	2 (4.3)	5 (3.8)
WBC Decrease	2 (3.9)	2 (6.1)	0	4 (3.1)
Dehydration	3 (5.9)	1 (3.0)	0	4 (3.1)
Vomiting	0	3 (9.0)	1 (2.2)	4 (3.1)
Leukemia, Recurrent	0	3 (9.0)	1 (2.2)	4 (3.1)
Febrile Neutropenia	2 (3.9)	1 (3.0)	0	3 (2.3)
Osteonecrosis	2 (3.9)	0	0	2 (1.5)
Pain in Extremity	2 (3.9)	0	0	2 (1.5)

Source: FDA Clinical Reviewer's Analysis

7.3.3 Dropouts and/or Discontinuations

In the pooled patient population, 4.6% of subjects discontinued treatment due to adverse events, 3.8% discontinued treatment because of Grade ≥ 3 AEs. The majority of these were deemed unrelated to dasatinib. A total of 2 subjects (1.5%) discontinued treatment due to drug-related AEs (drug hypersensitivity: n=1, bone pain: n=1).

7.3.4 Significant Adverse Events

See Sections 7.3.2, 7.3.5 and 7.4.

7.3.5 Submission Specific Primary Safety Concerns

Adverse events of special interest were examined either because of their association with dasatinib in the currently approved indications or because they are recognized events with other drugs in the same class (tyrosine kinase inhibitors). Events of special interest include fluid retention, pulmonary arterial hypertension, hemorrhage, cardiac events, and fatigue. The table below summarizes the incidence of AEs of special interest that occurred in the pooled patient population.

Table 35. Adverse Events of Special Interest (Pooled Population)

	Newly Diagnosed Ph+ CP CML (n=84)				Imatinib Resistant/ Intolerant Ph+ CP-CML (n=46)		Total CP-CML (n=130)	
	Cohort 3a: Tablet (n=51)		Cohort 3b: PFOS (n=33)					
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Fluid Retention								
Superficial Edema[1]	9 (17.6)	0	12 (36.4)	1 (3.0)	13 (28.3)	0	34 (26.2)	1 (0.8)
Generalized Edema[2]	2 (3.9)	0	2 (6.1)	0	0	0	4 (3.1)	0
Other fluid Related								
Pleural Effusion	1 (2.0)	0	0	0	0	0	1 (0.8)	0
Pulmonary Edema	0	0	0	0	0	0	0	0
Pericardial Edema	0	0	0	0	0	0	0	0
Bleeding Events (Hemorrhage)								
GI Bleeding	6 (11.8)	1 (2.0)	0	0	2 (4.3)	1 (2.2)	8 (6.2)	2 (1.5)
CNS Bleeding	0	0	0	0	0	0	0	0
Other Hemorrhage[3]	11 (21.6)	0	7 (21.2)	0	9 (39.6)	0	27 (20.8)	0
Pulmonary Arterial Hypertension	1 (2.0)	0	0	0	1 (2.2)	0	2 (1.5)	0
Cardiac Disorders	3 (5.9)	0	2 (6.1)	0	1 (2.2)	0	6 (4.6)	0
CHF/Cardiac dysfunction	2 (3.9)	0	0	0	1 (2.2)	0	3 (2.3)	0
Fatigue	19 (37.3)	1 (2.0)	9 (27.3)	0	20 (43.5)	0	48 (36.9)	1 (0.8)

[1] Includes the following PT terms: edema peripheral, swelling face, eye edema, eyelid edema, face edema, eye swelling, lip swelling, orbital edema, testicular edema, mucosal edema, periorbital edema
[2] Includes the following PT terms: generalized edema, fluid retention
[3] Includes the following PT terms: epistaxis, hemorrhage other, gingival bleeding, hematoma
Source: FDA Clinical Reviewer's Analysis

Fluid Retention

Overall, in the pooled patient population, 34 subjects (26.2%) experienced superficial edema and 4 (3.1%) experienced generalized edema. The majority of these events were mild in severity with only one subject experiencing a Grade ≥3 event (Grade 3 periorbital edema). Two subjects in the newly diagnosed group and one subject in the imatinib resistant/intolerant group experienced cardiac dysfunction (Grade 1: n=2, Grade 2: n=1). One subject in the newly diagnosed treatment group experienced Grade 2 pleural effusion. There were no events of pulmonary edema or pericardial edema across all treatment groups.

Pulmonary Arterial Hypertension

One subject, an 11 year old male with newly diagnosed CP-CML, experienced Grade 1 pulmonary arterial hypertension 1016 days after starting treatment with dasatinib. No dose modifications were made as a result of this AE. This subject experienced full resolution of this AE by the time of his next evaluation one year later.

One subject with imatinib resistant/intolerant CP-CML, a 15 year old female, experienced Grade 1 pulmonary arterial hypertension 1014 days after starting treatment with dasatinib. No dose modifications were made as a result of this AE. This subject experienced full resolution of this AE by the time of her next evaluation one year later.

There were no Grade ≥ 3 events of pulmonary arterial hypertension across the pooled patient population.

Hemorrhage

Treatment-emergent bleeding events occurred in 35 (26.9%) of subjects. The majority of these were mild in severity. Two subjects experienced Grade ≥ 3 gastrointestinal bleeding. A summary of the bleeding related adverse events is provided in the table below.

Table 36. Bleeding Events (Pooled Population)

	Newly Diagnosed Ph+ CP CML (n=84)				Imatinib Resistant/ Intolerant Ph+ CP-CML (n=46)		Total CP-CML (n=130)	
	Cohort 3a: Tablet (n=51)		Cohort 3b: PFOS (n=33)					
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Bleeding Events (Hemorrhage)								
GI Bleeding	6 (11.8)	1 (2.0)	0	0	2 (4.3)	1 (2.2)	8 (6.2)	2 (1.5)
Gingival Bleeding	1 (2.0)	0	0	0	2 (4.3)	0	3 (2.3)	0
Epistaxis	5 (9.8)	0	4 (12.1)	0	5 (10.9)	0	12 (9.2)	0
Hematoma	2 (3.9)	0	3 (9.1)	0	0	0	11 (8.5)	0
Other bleeding	3 (5.9)	0	0	0	2 (4.3)	0	5 (3.8)	0

Source: FDA Clinical Reviewer's Analysis

Clinical Reviewer Comment: Drug-related adverse events of special interest in pediatric subjects were consistent with the known safety profile of dasatinib in adults with CP-CML. In general, these adverse events were less frequent than seen in the adult data.

7.4 Supportive Safety Results

Study CA180038 (COG ADVL0516)
Study CA180038 was a Phase 1 study of dasatinib in pediatric subjects with recurrent/refractory solid tumors or imatinib resistant Ph+ leukemia. This study enrolled 11 subjects with leukemia (9 with CML and 2 Ph+ ALL). This study explored doses of 50 mg/m^2 BID, 65 mg/m^2 BID and 85 mg/m^2 BID for 28 day cycles. Because this study used BID dosing, safety data was not pooled with the other studies used to support the proposed indication for this application.

Deaths
There were no deaths in subjects with CP-CML.

Adverse Events
All subjects with CP-CML experienced at least one adverse event. The most frequent adverse events in children <11 years included increased AST, anemia, nausea and rash. The most frequent adverse events in children 11 to <18 years included thrombocytopenia, neutropenia, anemia and headache.

Clinical Reviewer Comment: The safety results from Study CA180038 are consistent with the known safety profile of dasatinib and are supportive of the proposed indication.

7.4.1 Common Adverse Events

In the treatment naïve group, a total of 84 subjects (100%) experienced 2,549 adverse events. In the imatinib resistant/intolerant treatment group, a total of 45 subjects (97.8) experienced 1,546 adverse events. The most common TEAEs in all treatment groups were abdominal pain, diarrhea, headache, vomiting and pyrexia.

The table below depicts a summary of the most common TEAEs occurring in ≥20% of subjects.

Table 37. Treatment Emergent Adverse Events - Any Grade (Pooled Population)

Preferred Term , n(%)	Newly Diagnosed Ph+ CP CML (n=84)		Imatinib Resistant/ Intolerant Ph+ CP-CML (n=46)	Total CP-CML (n=130)
	Cohort 3a: Tablet (n=51)	Cohort 3b: PFOS (n=33)		
Abdominal Pain	33 (64.7)	18 (54.5)	31 (67.4)	82 (63.1)
Diarrhea	25 (49.0)	16 (48.5)	28 (60.9)	69 (53.1)
Headache	25 (49.0)	16 (48.5)	28 (60.9)	69 (53.1)
Vomiting	22 (43.1)	12 (36.4)	24 (52.5)	58 (44.6)
Pyrexia	23 (45.1)	14 (42.4)	19 (41.3)	56 (43.1)
Cough	16 (31.4)	11 (33.3)	24 (52.5)	51 (39.2)
Pain in extremity	11 (21.6)	14 (42.4)	24 (52.5)	49 (37.7)
Nausea	20 (39.2)	10 (30.3)	18 (39.1)	48 (36.9)
Neutropenia	20 (39.2)	14 (42.4)	8 (17.4)	42 (32.3)
Thrombocytopenia	16 (31.4)	19 (57.8)	6 (13.0)	41 (34.5)
Upper respiratory infection	16 (31.4)	11 (33.3)	12 (26.1)	39 (30.0)
Anemia	15 (29.4)	14 (42.4)	3 (6.5)	32 (24.6)
Nasopharyngitis	10 (19.6)	4 (12.1)	15 (32.6)	29 (22.3)
Arthralgia	10 (19.6)	7 (21.2)	12 (26.1)	29 (22.3)

Source: FDA Clinical Reviewer's Analysis

Grade 3-4 AEs were reported in 84 subjects (64.6%) in the pooled patient population. The most frequent Grade 3-4 AEs were neutropenia (28.5%) and thrombocytopenia (14.6%). The most frequent Grade ≥ 3 TEAEs are depicted in the table below.

Table 38. Grade ≥3 Treatment Emergent Adverse Events (Pooled Population)

Preferred Term, n(%)	Newly Diagnosed Ph+ CP CML (n=84)		Imatinib Resistant/ Intolerant Ph+ CP-CML (n=46)	Total CP-CML (n=130)
	Cohort 3a: Tablet (n=51)	Cohort 3b: PFOS (n=33)		
Neutropenia	16 (31.4)	8 (24.2)	13 (28.3)	37 (28.5)
Thrombocytopenia	8 (15.7)	8 (24.2)	3 (6.5)	19 (14.6)
Anemia	8 (15.7)	7 (21.2)	1 (2.2)	16 (12.3)
Fever	4 (7.8)	1 (3.0)	0	5 (3.8)
Diarrhea	0	2 (6.1)	3 (6.5)	5 (3.8)
Febrile Neutropenia	2 (3.9)	2 (6.1)	0	4 (3.1)
Hypokalemia	2 (3.9)	2 (6.1)	0	4 (3.1)
Hypertension	0	2 (6.1)	0	2 (1.5)

Source: FDA Clinical Reviewer's Analysis

Clinical Reviewer Comment: The incidence of hematologic adverse events, including neutropenia, thrombocytopenia and anemia was higher in the treatment-naïve patients, compared to those who were previously treated with imatinib.

7.4.2 Laboratory Findings

Serum electrolyte evaluations and liver and renal functional evaluations were done throughout the study periods (see Section 5.3 for schedule of assessments).

In the pooled patient population, 42% of subjects experienced elevated ALT and 45% experienced elevated AST. The majority of these laboratory abnormalities were mild in severity (Grade 1 or 2). Only 5 subjects (3.8%) experienced Grade ≥ 3 elevated ALT and no subjects experienced Grade ≥3 elevated AST. A total of 16 subjects (12.3%) experienced elevated creatinine. However, these were all mild in severity with no subjects experiencing Grade ≥3 elevated creatinine.

An overview of select chemistry adverse events is provided below.

Table 39. Select Chemistry Adverse Events (Pooled Population)

Toxicity, n(%)	Newly Diagnosed Ph+ CP CML (n=84)				Imatinib Resistant/ Intolerant Ph+ CP-CML (n=46)		Total CP-CML (n=130)	
	Cohort 3a: Tablet (n=51)		Cohort 3b: PFOS (n=33)					
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
ALT (High)	20 (39.2)	1 (2.0)	17 (51.5)	3 (9.1)	17 (37.0)	1 (2.2)	54 (41.5)	5 (3.8)
AST (High)	26 (50.9)	0	16 (48.5)	0	17 (37.0)	0	59 (45.4)	0
Total Bilirubin (High)	11 (21.6)	0	2 (6.1)	0	5 (10.9)	2 (4.3)	18 (13.8)	2 (1.5)
Creatinine (High)	5 (9.8)	0	4 (12.1)	0	7 (15.2)	0	16 (12.3)	0

Source: FDA Clinical Reviewer's Analysis

Clinical Reviewer Comment: The proportions of subjects in the pooled population who experienced hematologic AEs (neutropenia, thrombocytopenia, anemia, leukopenia, etc.) and AEs related to abnormal serum chemistries were consistent with the known effects of dasatinib. Overall, most subjects experienced hematologic laboratory abnormalities. However, the majority of these were mild in severity. Leukopenia and thrombocytopenia occurred more frequently in subjects who with newly diagnosed disease.

7.4.3 Vital Signs

In studies CA180018 and CA180226, vital signs including weight, blood pressure, heart rate and oxygen saturation were monitored and recorded per the institutional standard of care during screening and treatment visits. No formal analyses of vital signs were performed. There were no trends of clinical relevance were noted with the use of dasatinib.

7.4.4 Electrocardiograms (ECGs)

Study 180018
ECGs were performed at baseline, at Day 10 ± 2 days of Cycle 1, at Day 10 ± 2 days of any course in which the dose was escalated and at the end of treatment. The majority of subjects had a decline in QTc from baseline in the -60 to 0 msec range. No subject had a QTc >500 msec.

Study 180226
A 12-lead ECG to determine baseline QTc was done 2 weeks prior to initiation of study therapy and was repeated during Week 2. All subjects who underwent a dose escalation were required to have another ECG at that dose. Additional ECGs were done at the investigator's discretion to ensure subject safety.

There was an overall trend towards a decrease in QTc from baseline in the -60 to 0 msec range. However, the median QTc change from baseline was 7.0 msec in Cohort 1 and 11.0 msec in Cohort 3. No subjects in Cohorts 1 or 3 had a QTc >500 msec.

7.4.5 Special Safety Studies/Clinical Trials

None.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Study CA180018 evaluated dose tolerability by underlying disease (assigned strata) and by individual subject. This study evaluated doses up to 120 mg/m^2 once daily. Of the 58 treated subjects, there were two DLTs, which both occurred in stratum 4 (Ph- ALL, Ph- AML). One subject experienced Grade 4 anaphylaxis 5 hours after the first dose of study drug (60 mg/m^2). One subject who was being treated with a dose of 120 mg/m^2 experienced an upper GI bleed on Day 6 of study treatment (platelet count at the time was 16,000/µL). Since no cohort had >33% DLTs reported, an MTD was not established for any stratum.

There were no DLTs in any subjects with CP-CML at doses up to 80 mg/m^2. In general, the proportion of subjects with drug-related SAEs and the proportion with Grade 3 - 4 neutropenia were higher in subjects in the 80 mg/m^2 dose cohort compared with the 60 mg/m^2 dose cohort. A summary of the major safety findings for subjects with CP-CML in this study is provided in the table below.

Table 40. Study 180018 - Summary of Safety by Dose

	Stratum 1: CP-CML	
	60 mg/m2 N=11	80 mg/m2 N=6
# of Subjects with any AE	11 (100.0)	6 (100.0)
Grade 3/4 AEs	4 (36.4)	2 (33.3)
Deaths	0	0
Serious AEs	1 (9.1)	1 (16.7)
AEs Leading to Discontinuation	0	0
Adverse Events of Special Interest		
Fluid Retention	1 (9.1)	1 (16.7)
Pleural Effusion	0	0
Cardiac Disorders	0	1 (16.7)
Diarrhea	0	4 (66.7)
Nausea/Vomiting	4 (36.4)	3 (50.0)
Rash	2 (18.2)	3 (50.0)
Neutropenia	1 (9.1)	3 (50.0)
Thrombocytopenia	2 (18.2)	0

Source: FDA Clinical Reviewer's Analysis

7.5.2 Time Dependency for Adverse Events

Time dependency for adverse events has been integrated into the primary safety analyses. Overall, there were no clinically meaningful trends in the incidence of specific adverse events over time.

7.5.3 Drug-Demographic Interactions

The table below summarizes the incidence of select adverse reactions by age.

Table 41. Select Adverse Reactions by Age (Pooled Population)

System Organ Class (%) Preferred Term (%)	Treatment-Naïve Ph+ CP-CML (n=84)		Imatinib Resistant/ Intolerant Ph+ CP-CML (n=44)		Total CP CML (n=128)	
	< 12 yrs (n=40)	12 – 18 yrs (n=44)	< 12 yrs (n=18)	12 – 18 yrs (n=26)	< 12 yrs (n=58)	12 – 18 yrs (n=70)
Total # of subjects with an event	40 (100.0)	43 (97.7)	18 (100.0)	24 (92.3)	58 (100.0)	67 (95.7)
Gastrointestinal Disorders	**28 (70.0)**	**36 (81.8)**	**18 (100.0)**	**23 (88.5)**	**46 (79.3)**	**59 (84.3)**
Diarrhea	18 (45.0)	23 (52.3)	13 (72.2)	14 (53.8)	31 (53.4)	37 (52.9)
Vomiting	21 (52.5)	13 (29.5)	11 (61.1)	12 (46.2)	32 (55.2)	25 (35.7)
Nausea	15 (37.5)	15 (34.1)	6 (33.3)	11 (42.3)	21 (36.2)	26 (37.1)
Abdominal Pain	14 (35.0)	13 (29.5)	12 (66.7	6 (23.1)	26 (44.8)	19 (27.1)
Constipation	6 (15.0)	8 (18.2)	5 (27.8)	2 (7.7)	11 (19.0)	10 (14.3)
General Disorders	**26 (65.0)**	**26 (59.1)**	**16 (88.9)**	**12 (46.2)**	**42 (72.4)**	**38 (54.3)**
Pyrexia	20 (50.0)	15 (34.1)	10 (55.6)	7 (26.9)	30 (51.7)	22 (31.4)
Fatigue	10 (25.0)	7 (15.9)	9 (50.0)	5 (19.2)	19 (32.8)	12 (17.1)
Skin and Subcutaneous Tissue Disorders	**25 (62.5)**	**25 (56.8)**	**13 (72.2)**	**15 (57.7)**	**38 (65.5)**	**40 (57.1)**
Rash	11 (27.5)	14 (31.8)	7 (38.9)	6 (23.1)	18 (31.0)	20 (28.6)
Pruritus	8 (20.0)	3 (6.8)	3 (16.7)	3 (11.5)	11 (19.0)	6 (8.6)
Urticaria	3 (7.5)	3 (6.8)	4 (22.2)	1 (3.8)	7 (12.1)	4 (5.7)
Musculoskeletal and Connective Tissue Disorders	**23 (57.5)**	**25 (56.8)**	**14 (77.8)**	**15 (57.7)**	**37 (63.8)**	**40 (57.1)**
Pain in extremity	15 (37.5)	10 (22.7)	12 (66.7)	11 (42.3)	27 (46.6)	21 (30.0)
Arthralgia	7 (17.5)	10 (22.7)	5 (27.8)	6 (23.1)	12 (20.7)	16 (22.9)
Myalgia	6 (15.0)	3 (6.8)	4 (22.2)	1 (3.8)	3 (5.2)	4 (5.7)
Cardiac Disorders	**4 (10.0)**	**3 (6.8)**	**2 (11.1)**	**3 (11.5)**	**6 (10.3)**	**6 (8.6)**
Palpitations	0	1 (2.3)	2 (11.1)	1 (3.8)	2 (3.4)	2 (2.9)
LV Dysfunction	1 (2.5)	0	0	1 (3.8)	2 (3.4)	2 (2.9)
Diastolic Dysfunction	1 (2.5)	0	0	0	1 (1.7)	0
Arrhythmia	1 (2.5)	0	0	1 (3.8)	1 (1.7)	1 (1.4)
Blood and Lymphatic System Disorders	**20 (50.0)**	**25 (56.8)**	**3 (16.7)**	**9 (34.6)**	**23 (39.7)**	**34 (48.6)**
Thrombocytopenia	11 (27.5)	9 (20.5)	2 (11.1)	4 (15.4)	13 (22.4)	13 (18.6)
Neutropenia	12 (30.0)	13 (29.5)	2 (11.1)	5 (19.2)	14 (24.1)	18 (25.7)
Anemia	4 (10.0)	11 (25.0)	0	3 (11.5)	4 (6.9)	14 (20.0)
Events of Special Interest						
Peripheral Edema	3 (7.5)	1 (2.3)	3 (16.7)	2 (7.7)	6 (10.3)	3 (4.3)
Facial Edema	1 (2.5)	2 (4.5)	1 (5.6)	0	2 (3.4)	2 (2.9)
Edema	1 (2.5)	1 (2.3)	0	0	1 (1.7)	1 (1.4)
Pulmonary Edema	0	0	0	0	0	0
Epistaxis	3 (7.5)	6 (13.6)	1 (5.6)	4 (15.4)	4 (6.9)	10 (14.3)
Hematoma	2 (5.0)	3 (6.8)	1 (5.6)	0	3 (5.2)	3 (4.3)
Hemorrhage	0	2 (4.5)	0	0	0	2 (2.9)

Source: FDA Clinical Reviewer's Analysis, Adapted from ISS

Clinical Reviewer Comment: In general, adverse events were equally distributed throughout the age spectrum. Younger subjects experienced slightly more vomiting,

abdominal pain, and general disorders (including pyrexia and fatigue) than the older subjects. Older subjects experienced more anemia than the younger patients. However, the differences are difficult to interpret due to the low sample sizes and overall event rates. These findings do not alter the overall safety profile of dasatinib in these age subgroups.

7.5.4 Drug-Disease Interactions

Not applicable.

7.5.5 Drug-Drug Interactions

Specific drug interaction studies with dasatinib have only been conducted in adults. No new information in pediatric subjects is available.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Not applicable.

7.6.2 Human Reproduction and Pregnancy Data

No pregnancies were reported in the pediatric studies. Exposure to dasatinib during pregnancy has not been permitted in the clinical development program.

7.6.3 Pediatrics and Assessment of Effects on Growth

Negative effects on growth and development have previously been reported in non-clinical studies of dasatinib as well as clinical studies of imatinib in children.

Adverse Events
The table below depicts the incidence of adverse events related to bone growth and development. There were no Grade 3 or 4 Growth and Development Adverse Events.

Table 42. Adverse Events Related to Growth and Development (Pooled Population)

	Newly Diagnosed Ph+ CP CML (n=84)				Imatinib Resistant/ Intolerant Ph+ CP-CML (n=46)		Total CP-CML (n=130)	
	Cohort 3a: Tablet (n=51)		Cohort 3b: PFOS (n=33)					
Toxicity, n(%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Epiphyses Delayed Fusion	0	0	0	0	1 (2.2)	0	1 (0.8)	0
Osteopenia	0	0	0	0	1 (2.2)	0	1 (0.8)	0
Gynecomastia	0	0	1 (30.3)	0	1 (2.2)	0	2 (1.5)	0
Growth Retardation	1 (1.9)	0	0	0	0	0	1 (0.8)	0

Source: FDA Clinical Reviewer's Analysis

Long-term Safety Effects on Growth and Development

The effects of dasatinib on growth and development and bone metabolism is part of the long term safety assessment, assessed annually while subjects is on study therapy and for 5 years after discontinuation of dasatinib. To date, dasatinib administered to pediatric subjects appears to have no clinically significant impact as measured by increases or decreases in Z-scores for weight, height or BMI, compared to reference ranges during the study.

Reviewer Comment: The long term effects of dasatinib on growth and development will require close monitoring, particularly as patients will likely be exposed to prolonged durations of treatment.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose

Two subjects in the pooled patient population experienced accidental overdoses.

1. Subject 180226 (b) (6) 6 year old female who was administered 100 mg/day of dasatinib instead of the protocol dose 55 mg/day. No symptoms, sequelae or adverse events were observed and the subject did not receive any treatment for this event. No action was taken related to the study drug and the previous dose was resumed.

2. Subject 180226 (b) (6) 16 year old female accidently took a double dose of dasatinib (200 mg) after forgetting to take her study drug (100 mg/day) several days before. No symptoms, sequelae or adverse events were observed and the subject did not receive any treatment for this event. No action was taken related to the study drug and the previous dose was resumed.

Drug Abuse Potential
There is no evidence of any dependence potential with dasatinib use.

Withdrawal and Rebound
No formal studies of rebound or withdrawal have been conducted with dasatinib. No particular events have been reported in the pediatric studies in patients who had a transient or definite withdrawal of dasatinib therapy.

7.7 Additional Submissions / Safety Issues

(b) (4)

8 Postmarket Experience

Dasatinib was first approved for the treatment of adult subjects with CML or Ph+ ALL who are resistant or intolerant to imatinib on 28-Jun-2006 by the US FDA. Dasatinib was subsequently approved in other countries and is currently marketed worldwide in over 60 international countries including the EU, Japan, and Canada.

As reported in Section 5.1 in Periodic Benefit-Risk Evaluation Report No. 4 (28-Jun-2015 through 27-Jun-2016), the estimated cumulative post-authorization exposure reporting period 28-Jun-2006 through 31-Mar-2016 is calculated to be = (b) (4) patient exposure years. Cumulatively, approximately (b) (4) subjects have enrolled in Company-sponsored clinical trials, with (b) (4) patients exposed to dasatinib.

Approximately, (b) (4) total subjects have been exposed to dasatinib under Expanded Access Programs (EAPs; CA180325). Cumulatively, (b) (4) subjects have been exposed to dasatinib while participating in an ISR/ISTs supported by the Company. Therefore, in total, approximately (b) (4) subjects have been exposed to dasatinib from 04-Nov-2003 to 27-Jun-2016.

Based on routine pharmacovigilance activities conducted by BMS Global Pharmacovigilance and Epidemiology, review of post-marketing data confirms that the safety profile of dasatinib remains favorable and similar to the profile established during clinical trials.

9 Appendices

9.1 Literature Review/References

1. Ries LG, Smith M, Gurney JG, et al. Cancer Incidence and Survival among Children and Adolescents. United States SEER Program 1975-1995. National Cancer Institute, vol.99. 1999: 46-49.
2. Hijiya N, Millot F, Suttorp M. Chronic myeloid leukemia in children: clinical findings, management and unanswered questions. *Pediatr Clin North Am* 2015;62(1):107-119.
3. Gambacorti-Passerini C, Aroldi A, Cordani N, et al. Chronic myeloid leukemia: second-line drugs of choice. *Am J Hematol.*2016;91(1):67-75.
4. Hughes T, Deininger M, Hochhaus A, et al., Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: review and recommendations for harmonizing current methodology for detection of BCR-ABL transcripts and kinase domain mutations and for expressing results. *Blood.* 2006;108:28-37.

9.2 Labeling Recommendations

Labeling negotiations are ongoing.

9.3 Advisory Committee Meeting

This application was not taken to an Oncologic Drugs Advisory Committee.

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/s/

RACHEL E ERSHLER
10/16/2017

NICOLE J GORMLEY
10/16/2017

THOMAS T LY
10/16/2017

LEI NIE
10/16/2017

THOMAS E GWISE
10/16/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21986Orig1s020

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review	
NDA	21986 (SDN 1543, eCTD 0132) / (b) (4)
Type/Category	Supplement 20 / Original
Submission Date	09/14/2017 / 05/09/2017
PDUFA	11/09/2017
Brand Name	SPRYCEL®
Generic name	Dasatinib
Formulation and Strength	Film coated tablet, 20 mg, 50 mg, 70 mg, and 100 mg (b) (4)
Route of Administration	Oral
Applicant	Bristol Myers Squibb
Proposed New Indication	Treatment of pediatric patients with Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in chronic phase.
Approved Indications	Treatment of • Newly diagnosed adults with Ph+ CML in chronic phase. • Adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib. • Adults with Ph+ acute lymphoblastic leukemia (ALL) with resistance or intolerance to prior therapy.
Proposed Dosing Regimen	Tablet: 60 mg/m^2 once daily. (b) (4)
Approved Dosing Regimen	• Ph+ CML in chronic phase: 100 mg once daily. • Accelerated or myeloid or lymphoid blast phase Ph+ CML or Ph+ ALL: 140 mg once daily.
OCP Divisions	Division of Clinical Pharmacology V (DCPV) Division of Pharmacometrics (DPM)
OND Division	Division of Hematology Products (DHP)
OCP Primary Reviewers	Yuhong Chen, MD and Ph.D.; Youwei Bi, Ph.D.
OCP Team Leaders	Stacy S. Shord, Pharm.D.; Justin C. Earp, Ph.D.

Table of Contents

List of Tables

List of Figures

1. EXECUTIVE SUMMARY

The applicant is seeking the approval of dasatinib for the treatment of pediatric patients with Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. The proposed dose is 60 mg/m^2 once daily (QD) for the commercial tablet (Supplement 20) (b) (4) (b) (4) Weight-tiered dosing (b) (4) The efficacy and safety of dasatinib is supported by Study CA180226, with additional safety data provided from Study CA180018 and Study CA180038.

The dose of 60 mg/m^2 QD as a tablet demonstrated an overall favorable benefit-risk profile. In 51 pediatric patients with newly diagnosed Ph+ CML in chronic phase, a complete cytogenetic response (CCyR) of 96% (95% CI: 86, 99) and a major molecular response (MMR) of 74% (95% CI: 60, 86) was observed with a minimum follow-up of 24 months. In 46 pediatric patients who received prior imatinib therapy, a CCyR of 83% (95% CI: 67, 92) and a MMR of 89% (76, 96) was observed with a minimum follow-up period of 24 months. The exposure was similar at this dose as compared to adults following a dose of 100 mg QD, supporting the tolerability of dasatinib in this pediatric population. No new safety signals were observed in the pediatric population. The proposed tablet dose of 60 mg/m^2 QD in pediatric patients is approvable from a clinical pharmacology perspective.

(b) (4)

1.1. Recommendations

The Office of Clinical Pharmacology recommends approval of Supplement 20 of NDA 21986 (b) (4) (b) (4) provided that the applicant and the Agency come to a mutually satisfactory agreement regarding the labeling language.

Signatures:

Yuhong Chen, MD & Ph.D. Clinical Pharmacology Reviewer Division of Clinical Pharmacology V	**Youwei Bi, Ph.D.** Pharmacometrics Reviewer Division of Pharmacometrics
Stacy S. Shord, Pharm.D. Team Leader Division of Clinical Pharmacology V	**Justin C. Earp, Ph.D.** Acting Team Leader Division of Pharmacometrics
Atiqur Rahman, Ph.D. Division Director Division of Clinical Pharmacology V	

CC: DHP: RPM – W Lee; MO – R Ershler; MTL – N Gormley

DCPV: DDD – B Booth
DPM: DD – Yaning Wang

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

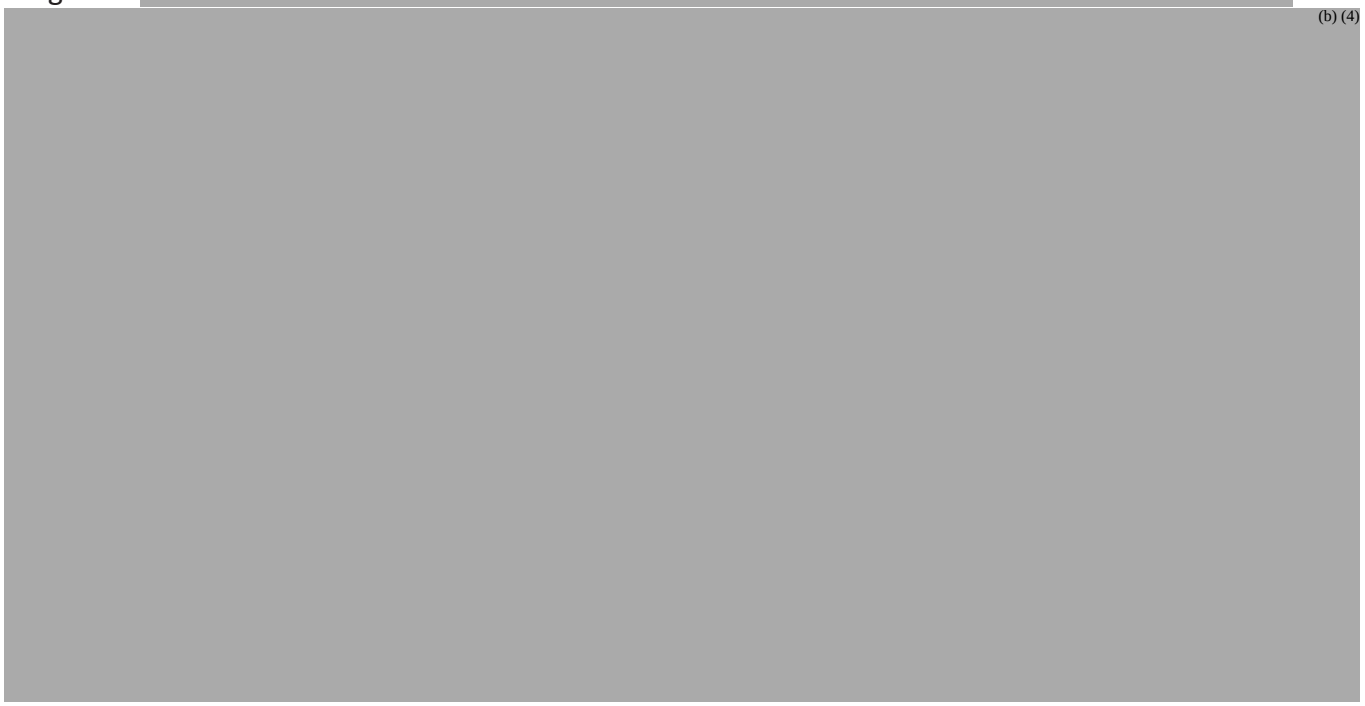
2.1. Pharmacology and Clinical Pharmacokinetics

Dasatinib (SPRYCEL®) is a tyrosine kinase inhibitor. It is approved for the treatment of chronic phase Ph+ CML in adults at a dose of 100 mg QD; and accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL in adults at a dose of 140 mg QD. For brevity, only information related to the current submissions is summarized.

- The C_{max} and AUC of the dasatinib tablet were approximately dose proportional following single and multiple-dose administration in pediatric patients.
- No clinically meaningful effect of age or disease type on dasatinib PK in pediatric patients was identified.
- (b) (4)

- (b) (4)

Figure 1. (b) (4)



- A weight-tiered dosing is proposed (Table 1). The proposed dose for each weight tier is predicted to provide similar exposure to the tablet dose of 60 mg/m^2 in pediatric patients (see Table 8).

Table 1. Dosage of SPRYCEL for Pediatric Patients

Body Weight (kg)[a]	**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

2.2. Dosing and Therapeutic Individualization

2.2.1 General dosing

The recommended dose for the treatment of pediatrics with newly diagnosed CML is 60 mg/m^2 QD administered orally as an intact commercial tablet (b) (4) (b) (4) Dasatinib is currently available as 20, 50, 70 and 100 mg tablets. (b) (4) (b) (4) may be taken without regard to food. The proposed dosing regimen for the tablet is acceptable based on the efficacy and safety data from Study CA180226.

(b) (4)

2.2.2 Therapeutic individualization

The apparent oral clearance of dasatinib is correlated with body surface area (BSA), and individual dosing in pediatric patients is based on BSA. Individual dosing should also be based on concomitant medications regarding potential drug-drug interactions as labeled for adults.

2.3. Outstanding Issues

(b) (4)

Reviewer's comment: (b) (4)

(b) (4)

2.4. Summary of Labeling Recommendations

In general, the applicant provided adequate clinical pharmacology information to support the product labeling. We recommend the following labeling concepts to be included in the final package insert:

- Modified doses in the proposed weight-tiered dosing section (Section 2).
- The PK data for pediatric patients in section 12.3.
- Do not crush the commercial tablet throughout the labeling. The available PK data following administration of the commercial tablet crushed shows the exposure is ~20% lower than the intact tablet.

(b) (4)

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1. Overview of the Product and Regulatory Background

Dasatinib received FDA approval for the following indications:

- 06/28/2006: Treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib.
- 10/28/2010: Treatment of adults with newly diagnosed Ph+ CML in chronic phase.

A pediatric Written Request (WR) was issued on 9/17/2007, followed by Amendment #1 on 10/13/2009, Amendment #2 on 07/23/2013, Amendment #3 on 05/29/2014 and Amendment #4 on 03/04/2015. The WR described the development of dasatinib in pediatric patients with imatinib-resistant chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia (CP, AP, and BP CML) (b) (4) The data submitted in this application package is in partial response to the WR.

This submission includes the results of four trials. The applicant also submitted a population PK and ER exposure-response (E-R) analysis report.

1. Study CA180226: A Phase II Study of Dasatinib Therapy in Children and Adolescents with Newly Diagnosed Chronic Phase CML or with Ph+ leukemias Resistant or Intolerant to Imatinib.
2. Study CA 180038: A Phase I Study of BMS-354825 (Dasatinib) in Children with Recurrent/Refractory Solid Tumors or Imatinib Resistant Ph+ Leukemia.

3. Study CA180018: Phase I Study of SRC/ABL Tyrosine Kinase Inhibitor Dasatinib (BMS-354825) in Children and Adolescents with Relapsed or Refractory Leukemia.

(b) (4)

3.2. General Pharmacological and Pharmacokinetic Characteristics

Please refer to the SPRYCEL® labeling and the clinical pharmacology review of the original NDA 21986 submission (DARRTS ID: 2749479) for a description of the PK characteristics of dasatinib in adult patients and other specific populations.

- Oral administration of dasatinib to pediatric patients resulted in systemic exposures that were dose proportional across the dose range of 60 mg/m^2 to 120 mg/m^2. This finding was consistent with the established dose proportionality over the dose range of 15 mg/day to 240 mg/day in adult patients.
- No clinically meaningful effect of age or disease type was observed on the PK of dasatinib in pediatric patients.
- The Tmax was observed between 0.5 hours and 6 hours and the half-life was 2 hours to 5 hours.
- The geometric mean (CV%) of body weight normalized clearance patients is 5.9 (30.5%) L/h/kg. In pediatric patients with a dosing regimen of 60 mg/m^2, the geometric mean (CV%) steady-state plasma average concentration of dasatinib is
    - 13.8 (76.6%) ng/mL for patients 2 to < 6 years old,
    - 16.5 (75.5%) ng/mL for patients 6 to < 12 years old, and
    - 17.9 (77.4%) ng/mL for patients 12 years and older.

(b) (4)

Table 2. (b) (4)

(b) (4)

3.3. Clinical Pharmacology Questions

3.3.1. Is the proposed general dosing regimen for the intact commercial tablet appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dosing regimen of 60 mg/m^2 QD as the intact tablet is appropriate for pediatric patients with Ph+ CML in chronic phase. The dose demonstrates an acceptable safety profile and effectiveness in pediatric patients with Ph+ CML in chronic phase. No new safety signals were observed in the pediatric population and the exposure following the proposed dosing regimen is similar to the exposure following a 100 mg QD dose in adult population. A weight-tiered dosing approach will be included in the labeling (See Section 3.3.3).

Dose Selection

The intact tablet dose of 60 mg/m^2 was selected based on the overall efficacy, safety and PK results from a dose finding study in pediatrics (Trial CA180018). The trial enrolled 58 subjects into three strata, which all utilized a starting dose of 60 mg/m^2 QD. Stratum 1 (Ph+ CML in chronic phase) and Stratums 2 & 3 (Ph+ ALL or accelerated phase or blast phase CML) evaluated dasatinib in pediatric patients at doses ranging from 60 mg/m^2 to 80 mg/m^2 QD. Favorable response rates in pediatrics with Ph+ CML in chronic phase were achieved at a dose of 60

mg/m^2 QD (MCyR of 82% and CCyR of 73%). In addition, a dose of 60 mg/m^2 QD compared to a dose of 80 mg/m^2 QD was better tolerated. The study showed that the exposure of dasatinib and its minor metabolite at a dose of 60 mg/m^2 in pediatric patients was similar to that observed in adults at the approved dose of 100 mg QD.

Efficacy

The efficacy of dasatinib was evaluated in 51 pediatric patients with newly diagnosed Ph+ CML in chronic phase (Trial CA180226, cohort 3a) and 46 pediatric patients with Ph+ CML in chronic phase who received prior imatinib therapy (Trial CA180226 and Trial CA180018)**.** Ninety-one of these 97 patients were administered a tablet dose of 60 mg/m^2 QD. Patients were treated until disease progression or unacceptable toxicity. Table 3 summarizes the efficacy of dasatinib in pediatric patients with Ph+ CML in chronic phase.

The median age was 13.5 years (2 years to 20 years) for the 46 patient with imatinib resistant or intolerant CML. The median duration of follow-up was 5.2 years (range 0.5 to 9.3 years).

The median age was 12.8 years (1.9 year to 17.8 years) for the 51 patients with newly diagnosed CML. The median duration of follow-up was 4.5 years (range 1.3 to 6.4 years). The median time to MMR (95% CI) was 8.9 months (95% CI: 6.2, 11.7).

Table 3. Summary of Efficacy Results for Dasatinib in Pediatric Patients with Ph+ CML in Chronic Phase with a Minimum Follow-Up of 24 Months

	Newly Diagnosed (n=51)	Prior Imatinib (n=46)
Complete Cytogenetic Response (CCyR)	96.1% (86.5, 99.5)	82.6% (68.6, 92.2)
Major Molecular Response (MMR)	74.5% (60.4, 85.7)	52.2% (36.9, 67.1)

Source: Summary of Clinical Efficacy, Table 2.3-1.

Safety

The dasatinib safety profile in pediatric patients is similar to that reported in adults. No new safety signals were identified in the pediatric population. No cases of pleural or pericardial effusion, pulmonary edema or hypertension, or arterial pulmonary hypertension related to dasatinib were observed in pediatric patients with Ph+ CML in chronic phase.

In Trial CA180226 cohort 3a (N=51), the dose interruption for hematological toxicity was 25.5% and the dose reduction for hematological toxicity was 7.8%. The dose interruption for non-hematological toxicity was 17.6%, and the dose reduction for non-hematological toxicity was 3.9%. The median time to dose reduction or interruption due to hematologic toxicity was 61

days (minimum 8 days, maximum 259 days) and the median time to dose reduction or interruption due to any toxicity was 79 days (minimum 8 days, maximum 983 days). In Study CA180226 cohort 1 (N=29), the dose interruption for hematological toxicity was 17.2% and the dose reduction for hematological toxicity was 10.3%. The dose interruption for non-hematological toxicity was 20.7%, and the dose reduction for non-hematological toxicity was 10.3%. The median time to dose reduction or interruption due to hematologic toxicity was 67 days (minimum 49 days, maximum 166 days) and the median time to dose reduction or interruption due to any toxicity was 104 days (minimum 38 days, maximum 811 days).

3.3.2. (b) (4)

(b) (4)

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(b) (4)

Table 4

(b) (4)

(b) (4)

Table 5. Summary of Baseline Covariates in Trial CA180226

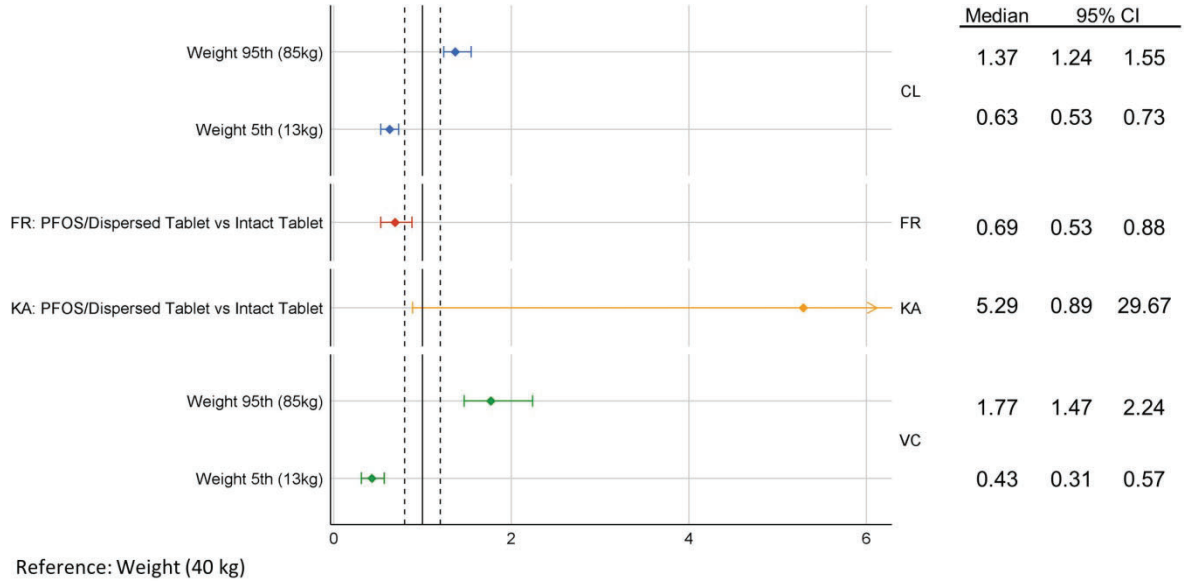
Subject Characteristic		Cohort 3a (N=51)	Cohort 3b (N=33)	Overall (N=84)
Age [years]	Mean (SD)	11.7 (4.10)	10.8 (4.87)	11.4 (4.41)
	Median	12	11	12
	Minimum, Maximum	1, 17	1, 17	1, 17
	Missing n (%)	0 (0.00)	0 (0.00)	0 (0.00)
Baseline Body Weight [kg]	Mean (SD)	41.8 (17.6)	45.5 (26.3)	43.3 (21.4)
	Median	38	38.7	38.4
	Minimum, Maximum	13, 91.1	11.9, 114	11.9, 114
	Missing n (%)	0 (0.00)	0 (0.00)	0 (0.00)
Baseline Body Surface Area [m^2]	Mean (SD)	1.3 (0.357)	1.33 (0.503)	1.31 (0.417)
	Median	1.27	1.25	1.27
	Minimum, Maximum	0.589, 2.13	0.542, 2.38	0.542, 2.38
	Missing n (%)	0 (0.00)	0 (0.00)	0 (0.00)
Steady State Time-averaged Concentration [ng/mL]	Mean (SD)	N/A	11.3 (2.91)	11.3 (2.91)
	Median	N/A	11.9	11.9
	Minimum, Maximum	N/A	3.61, 16.9	3.61, 16.9
	Missing n (%)	51 (100)	1 (3.03)	52 (61.9)
Baseline BCRABL Transcript Level [BCR-ABL/ABL ratio]	Mean (SD)	61.4 (28.1)	65.9 (32)	63.2 (29.6)
	Median	63.8	63.6	63.8
	Minimum, Maximum	4.78, 123	6.31, 144	4.78, 144
	Missing n (%)	0 (0.00)	0 (0.00)	0 (0.00)

Source: CSR of Trial CA180226, Table 3.3.2.2-2.

3.3.3. Are an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

Body weight is the most significant covariate of dasatinib clearance in pediatric patients with an allometric exponent for the effect of clearance estimated to be 0.41. The ratio of CL comparing a patient weighing 85 kg to a patient weighing 40 kg was estimated to be 1.4 (95% CI: [1.2, 1.6]) (Figure 2).

Figure 2. Covariate Effects on PPK Model Parameters of Dasatinib in Pediatric Patients



Weight-tiered dosing was proposed by the applicant to overcome the limitation on tablet strength and to reduce potential dosing errors. The weight-tiered dose selection was based on a comparison of the results between simulated exposure of weight-tiered dose and the target exposure of a tablet dose of 60 mg/m^2 QD. The exposure of weight-tiered dose is considered similar if the geometric mean of simulated steady-state exposure is within 20% of the target exposure.

Table 6 presents geometric means of the predicted Cavgss at proposed weight-tiered doses (with every 5 mg increment) and at the reference dose of 60 mg/m^2 tablet. The proposed weight-tiered dose 40, 60, 70 and 100 mg is expected to produce similar exposure compared to reference 60 mg/m^2 tablet in weight category [10kg, 20kg), [20kg, 30kg), [30kg, 45kg) and at least 45 kg, respectively.

Table 6. Comparison of Dasatinib Cavgss Achieved by WT-Tiered Tablet Dose and 60 mg/m^2 Tablet Dose

Weight Tier (kg)	Proposed Tablet Dose (mg)	Cavg. SS. Geom if dose using		Difference in Geo. Mean (%)	% Within 80% CI of Target Cavgss
		BSA (ng/mL)	Flat (ng/mL)		
10-15	40	12.5	14.5	+15.9	78.5
15-20	40	13.7	12.9	-5.9	80.7
(b) (4)					
20-25	60	14.9	17.2	+15.5	78.6
(b) (4)					
25-30	60	15.6	15.9	+1.6	80.2
30-35	70	16.3	17.3	+5.8	79.9
35-40	70	16.9	16.2	-4.1	80.1
(b) (4)					
45-50	100	17.9	20.9	+16.7	78.6
50-55	100	18.3	20.1	+9.9	79.9
55-60	100	18.6	19.4	+4.1	79.6

4. APPENDICES

4.1. Summary of Bioanalytical Method Validation and Performance

Plasma concentrations of dasatinib were determined using a validated LC/MS/MS. The assay is the same as the bioanalytical method used in prior original and supplement NDA submissions. The bioanalytical method was adequately validated with a calibration range of 1 ng/mL to 1000 ng/mL for dasatinib and was demonstrated long-term storage stability for samples in the current trials.

4.2. Clinical PK and PD Assessments

Trial CA180018: A dose finding study in pediatrics with relapsed or refractory leukemia was conducted to identify a dose for pediatrics. A dose of 60 mg/m^2 to 120 mg/m^2 QD with or

without food was administered. Table 7 provides a summary of the PK parameters by dose level and age group.

- Maximum plasma concentrations (C_{max}) of dasatinib were observed between 0.5 hours and 6 hours (T_{max}) following oral administration.
- The mean elimination half-life ranged from 2 hours to 5 hours across all dose levels and age groups.
- Oral administration of dasatinib to pediatric patients resulted in systemic exposures in terms of C_{max}, AUC_{last}, and AUC_{inf} that were consistent with dose proportionality in the dose range of 60 mg/m^2 to 120 mg/m^2.
- There was no statistical evidence of a difference in geometric means of dasatinib C_{max}, AUC_{last} and AUC_{inf} between children and adolescents at the different dose levels.

Table 7. Summary Statistics for Dasatinib Pharmacokinetic Parameters by Dose Level and Age Group in Trial CA180018

DOSE LEVEL (mg/m^2)	AGE GROUPS	Cmax (ng/mL) GEO.MEAN[N] (%CV)	Tmax (h) MEDIAN[N] (MIN-MAX)	AUC(0-T) (ng.h/mL) GEO.MEAN[N] (%CV)	AUC(INF) (ng.h/mL) GEO.MEAN[N] (%CV)	T-HALF (h) MEAN[N] (SD)
60	CHILDREN	110.6[11] (61.8)	1.1[11] (0.5-2.1)	295.0[10] (63.5)	313.9[10] (59.8)	2.4[10] (1.0)
	ADOLESCENTS	92.6[9] (50.6)	1.0[9] (0.5-4.0)	320.8[9] (59.1)	305.8[8] (60.9)	3.7[8] (1.6)
	TOTAL	102.1[20] (58.0)	1.0[20] (0.5-4.0)	307.0[19] (60.2)	310.3[18] (58.6)	3.0[18] (1.4)
80	CHILDREN	142.5[16] (80.2)	1.5[16] (0.5-3.2)	490.8[16] (96.7)	513.6[14] (99.2)	3.9[14] (1.9)
	ADOLESCENTS	116.5[8] (73.0)	1.1[8] (0.5-4.0)	488.1[8] (35.0)	605.1[5] (25.3)	5.1[5] (0.5)
	ABOVE 18 YRS	143.2[1] (.)	0.9[1] (0.9-0.9)	367.2[1] (.)	390.0[1] (.)	7.3[1] (.)
	TOTAL	133.6[25] (77.6)	1.1[25] (0.5-4.0)	484.3[25] (88.9)	527.8[20] (90.4)	4.4[20] (1.8)
100	INFANTS AND TODDLERS	30.6[1] (.)	0.5[1] (0.5-0.5)	100.8[1] (.)	127.7[1] (.)	2.5[1] (.)
	CHILDREN	111.2[9] (82.6)	1.1[9] (0.6-4.1)	373.5[8] (82.0)	429.1[7] (76.8)	4.6[7] (3.5)
	ADOLESCENTS	235.1[9] (59.0)	1.0[9] (0.5-6.0)	787.0[9] (76.2)	1008.9[7] (69.4)	4.5[7] (2.5)
	TOTAL	148.1[19] (75.0)	1.0[19] (0.5-6.0)	504.1[18] (89.6)	589.8[15] (86.2)	4.4[15] (2.9)
120	INFANTS AND TODDLERS	53.8[1] (.)	0.5[1] (0.5-0.5)	134.9[1] (.)	142.2[1] (.)	1.8[1] (.)
	CHILDREN	208.4[7] (78.5)	1.0[7] (0.9-2.2)	676.7[6] (99.9)	817.6[5] (93.7)	3.2[5] (1.9)
	ADOLESCENTS	123.3[2] (68.3)	1.6[2] (1.0-2.1)	526.1[2] (56.6)	547.8[2] (58.2)	3.5[2] (2.9)
	TOTAL	163.9[10] (87.6)	1.0[10] (0.5-2.2)	534.9[9] (103.9)	594.4[8] (101.5)	3.1[8] (1.9)

(1) Infants and toddlers with age<2 years old, children with age>=2 and <12 years old, adolescents with age>=12 and <18 years old

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Source: CSR of Trial CA180018, Table 10.2.1A.

Trial CA180038 is a phase 1 dose finding trial in pediatrics with recurrent or refractory solid tumors or imatinib resistant Ph+ leukemia. The administered dose range was 50 mg/m^2 to 110 mg/m^2 BID with or without food. Table 8 provides a summary for the PK parameters by dose and age group.

Table 8. Summary Statistics for Dasatinib Pharmacokinetic Parameters by Dose and Age Group in Pediatric Patients

Dose	Age group	N	Cmax (ng/mL) Geomean (CV%)	AUC(0-T) (ng.h/mL) Geomean (CV%)	AUC(0-INF) (ng.h/mL) Geomean (CV%)	Tmax (h) Med (min, max)	$T_{1/2}$ (h) Mean (SD)
50 mg/m^2 BID	Children (2 - < 11 years)	2	45.0 (31)	183.3 (11)	199.8 (12)	2.3 (0.6, 4.0)	2.1 (0.4)
	Adolescents (11 - < 18 years)	2	93.9 (70)	269.2 (21)	295.4 (14)	1.0 (0.5, 1.5)	2.5 (0.5)
	Total	4	65.0 (74)	221.1 (27)	242.9 (25)	1.1 (0.5, 4.0)	2.3 (0.4)
65 mg/m^2 BID	Children (2 - < 11 years)	3	119.0 (36)	265.2 (32)	277.0 (32)	0.5 (0.5, 2.0)	2.1 (5.9)
	Adolescents (11 - < 18 years)	1	244.1	610.1	621.7	1.0	5.4
	Total	4	142.4 (45)	326.7 (51)	338.9 (49)	0.8 (0.5, 2.0)	3.0 (1.6)
85 mg/m^2 BID	Children (2 - < 11 years)	3	110.1 (25)	417 (31)	431.1 (30)	2.0 (1.0, 2.0)	2.6 (1.1)
	Adolescents (11 - <18 years)	3	174.7 (30)	641.7 (50)	669.9 (48)	1.0 (0.5, 4.0)	3.7 (0.8)
	Total	6	138.7 (36)	517.0 (50)	537.4 (49)	1.5 (0.5, 4.0)	3.2 (1.1)
110 mg/m^2 BID	Children (2 - < 11 years)	1	110.1	258.8	--	1.0	--
	Adolescents (11 - < 18 years)	3	251.2 (56)	763.0 (26)	784.9 (25)	1.0 (0.3, 6.0)	3.7 (2.0)
	Late adolescents (≥ 18 years)	1	151.5	421.2	440.8	0.5	6.6
	Total	5	192.5 (63)	545.8 (47)	679.5 (34)[b]	1.0 (0.3, 6.0)	4.5 (2.2)[b]

Cmax = maximum concentration; CV% = percent coefficient of variation; AUC(0-T) = area under the concentration-time curve from Time 0; AUC(0-INF) = area under the concentration-time curve from Time 0 to infinity; Tmax = time to maximum concentration; Med = median; min = minimum; max = maximum; $T_{1/2}$ = half life; SD = standard deviation.

[a] N = 4

Source: CSR of Trial CA180038, Table 9.2.1.

Trial CA180226 is a phase II study of dasatinib in pediatrics with newly diagnosed CML in chronic phase or with Ph+ leukemias resistant or intolerant to imatinib. Sparse PK samples were collected from patients enrolled in Cohort 3b administered a PFOS dose of 72 mg/m^2 PFOS QD. The dasatinib concentration data from this trial was included in the population PK analysis detailed in section 4.3 of this review.

4.3. Population PK Analysis

4.3.1 Introduction

Population PK (PPK) analysis was conducted to characterize the dasatinib plasma concentration-time profile in pediatric patients with leukemia and solid tumors, to determine the effects of covariates on dasatinib PK parameters, (b) (4) As the available tablet strengths does not allow BSA-based dosing strategy to provide the exact same mg dose, the established PPK model was also used to determine the body weight-tiered doses for tablet (b) (4)

4.3.2 Model development and evaluation

The PPK analysis dataset included 104 pediatric patients (761 PK samples) from 2 phase 1 studies (CA180038 and CA180038) and 1 phase 2 study (CA180226). There are intensive dasatinib concentration data from 44 pediatric patients who took intact tablet and 9 patients who took crushed tablet in phase 1 study CA180018 which primarily supports characterization of dasatinib PK of intact tablets in pediatric patients. The sparse concentration data collected from 32 patients in cohort 3b in Trial CA180226 provides the basis of comparing the exposure between tablet and PFOS formulation. The analysis dataset included data for dasatinib tablet doses ranging from 60 mg/m^2 to 120 mg/m^2 QD as tablet and dasatinib 72 mg/m^2 QD as PFOS. About 9.5% of dasatinib concentration data was below the limit of quantitation. The formulation records in all 19 patients in phase 1 study CA180038 are missing.

The dasatinib PK profile was initially described using a two compartment model with first-order absorption and first-order elimination using NONMEM 7.3. The below limit of quantitation (BLQ) concentrations were included as censored observations in the likelihood calculation used for parameter estimation (method M3). Formulation is the only covariate with missing information, which was imputed as intact tablet in the analysis. The covariate effects tested in the full model include covariate effects of baseline bodyweight on clearance (CL) and volume of distribution (VC), and the effect of formulation on absorption rate (KA) and relative bioavailability (FR). In an relative bioavailability study in healthy adults, the crushed tablet and PFOS was shown to be 16% and 19% less bioavailable than the reference intact tablet, while PFOS and crushed tablet was determined to be bioequivalent. In a post-hoc statistical analysis comparing the exposure of dasatinib in pediatrics given tablets or crushed tablets in Trial CA180018, the point estimate of ratio of geometric mean AUCinf was 0.78 for the crushed tablet to the intact tablet. Thus, the crushed tablet and PFOS were combined into one category in the full covariate model.

The reviewer has the following comments regarding the final PPK model:

1. The BLQ observations were included as censored observations in the likelihood calculation used for parameter estimation in the final model. Although M3 method is expected to introduce less bias into parameter estimates, this approach tends to cause very high percentage of non-successful termination. It must be ensured the model estimation is stable, and consistent parameter estimates are obtained for the final model, especially when the simulation results was intended to be applied to compare exposure and select dose. 200 parallel retries with different initial estimates were conducted using PSN to assess the model stability and sensitivity of parameter estimates to initial estimates. There is considerable variability in the estimated relative bioavailability (FR_FPOS) comparing PFOS

to reference tablet. The FR_PFOS has a coefficient of variation (CV) of 19.3% among 25 retries with lowest objective function (OFV) and ranges from -0.60 to -0.24. As consistent parameter estimates cannot be achieved with the proposed final model with M3 approach, "LLOQ/2" method was explored as when the percentage of BLQ data is low (<=10%), "LLOQ/2" method gave similar results for the PK model and were in general more stable compared to M3 method. Similarly, 200 parallel retries were conducted to evaluate the model. The estimate of relative bioavailability (FR_PFOS) was consistent ranging from -0.39 to -0.37 and has a much smaller CV (1.4%) in the 25 retries with lowest OFV.

2. There are 19 patients (18.3%) with missing records of formulation from Trial CA180038. They were initially imputated as intact tablet in the original analysis. A sensitivity analysis was conducted to assess the effect of this imputation on the parameter estimation. And it was found estimates of relative bioavailability are almost exactly same (~0.3% difference) when the missing formulation was imputed as the reference tablet or categorized as a new group "missing"; however, the effect of PFOS on absorption rate is 74% larger when missing formulation was imputed as intact tablet in the analysis.
3. The model estimates of the updated PPK model using "LLOQ/2" approach are shown in Table 9. The clearance and volume of distribution were estimated with good precision with relative standard error less than 15%. There is relatively large variability in the parameter estimates of effect of PFOS on bioavailability and absorption rate, likely due to sparse PK data of PFOS formulation. Prediction-corrected visual predictive check stratified by formulation (Figure 3) showed that the final model adequately described the observed PK profile of dasatinib in pediatric patients. No signs of model misspecification were identified in the goodness-of-fit plots (Figure 4). However, due to high shrinkage of inter-individual variability (IIV) of KA and FR (>27%), the individual prediction (IPRED) and individual weighted residual (IWRES) have low power to diagnose model misspecifications. The dose-normalized (DN) AUC_{inf} in patients who took intact tablet in phase 1 study CA180018 were calculated based on simulations and observations and compared with each other to further evaluate the model's ability to predict dasatinib exposure. Both geometric mean and CV for DN AUCinf based on simulations are comparable to those based on observations (Figure 5).

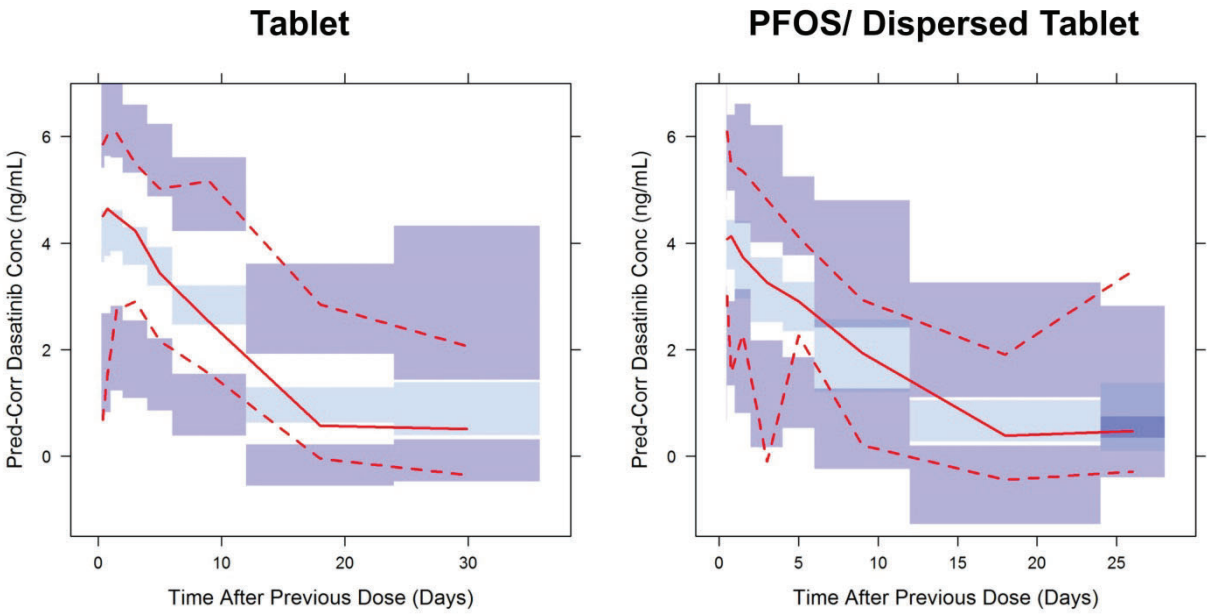
Overall, the model evaluation shows the updated PPK model is able to adequately describe the PK profile of dasatinib in pediatric patients and can be applied for evaluation of weight-tiered dosing regimen of tablet (b) (4) (b) (4)

Table 9. Parameter Estimates of the Final PPK Model

Parameter [Units]	Parameter Estimate	Standard Error (RSE%)	95% Confidence Interval[a]
Fixed Effects			
CL/F_{REF} [L/h]	225	21.9 (9.7%)	195 – 256
VC/F_{REF} [L]	769	111 (14.4%)	645 – 914
Q/F [L/h]	36.5	17.2 (47.1%)	25.7 – 44.9
VP/F [L]	322	53.4 (16.6%)	229 – 419
KA_{REF}	1.51	0.51 (33.8%)	1.01 – 2.57
CL_{BW}	0.419	0.117 (27.9%)	0.288 – 0.58
VC_{BW}	0.76	0.181 (23.8%)	0.511 – 1.07
FR_{PFOS} [b]	-0.375	0.143 (38.1%)	-0.636 – -0.124
$FR_{Missing}$	0 FIX		
KA_{PFOS} [b]	1.12	0.468 (41.8%)	-0.112 – 3.39
$KA_{Missing}$	-0.948	0.255 (26.9%)	-1.65 – 0.0172
Random Effects[c]			
ω^2KA [-]	1.85 (1.36)	0.579 (31.3%)	1.23 – 2.84
ω^2FR [-]	0.216 (0.46)	0.0613 (28.4%)	0.0753 – 0.373
ω^2FR, IOV [-]	0.109 (0.33)	0.0565 (51.8%)	0 – 0.223
Residual Error			
θLADD [-]	0.823	0.0164 (2%)	0.732 – 0.894

a. Confidence intervals were generated based on 1000 bootstrap results.
b. $KA = KA_{REF} * \exp(KA_{PFOS})$ and $FR = \exp(FR_{PFOS})$ if formulation is PFOS
c. Eta shrinkage (%): ETA_KA: 27.3%, ETA_FR: 27.9%

Figure 3. Prediction-corrected Visual Predictive Check for Dasatinib Stratified by Formulations



Red solid lines are median percentiles for observed data. Red dashed lines are 5th and 95th percentiles for observed data. Light blue area is the 95% confidence interval (CI) around the simulated median. Dark blue area is the 95% confidence interval (CI) around the simulated 5th and 95th percentiles.

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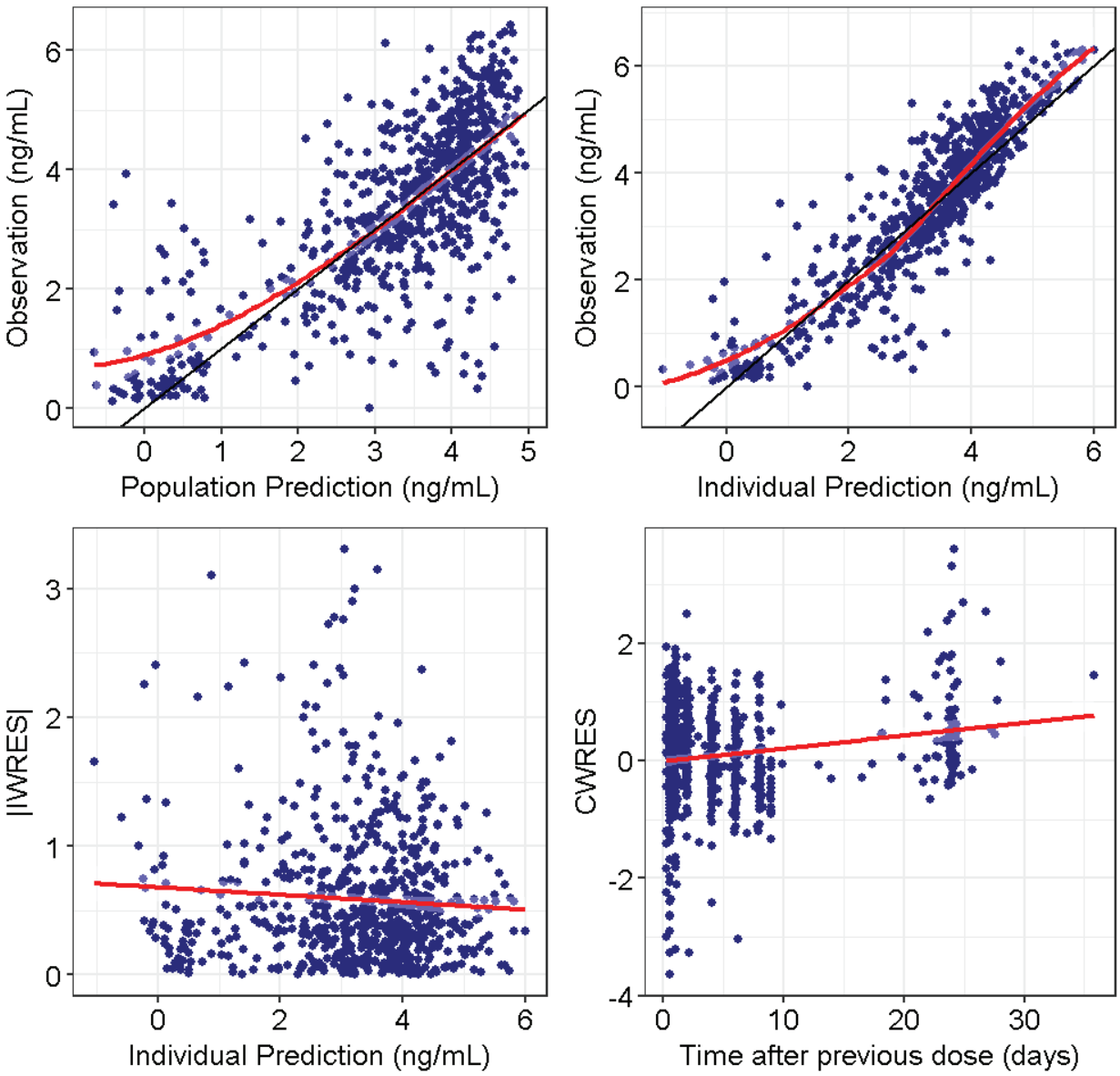
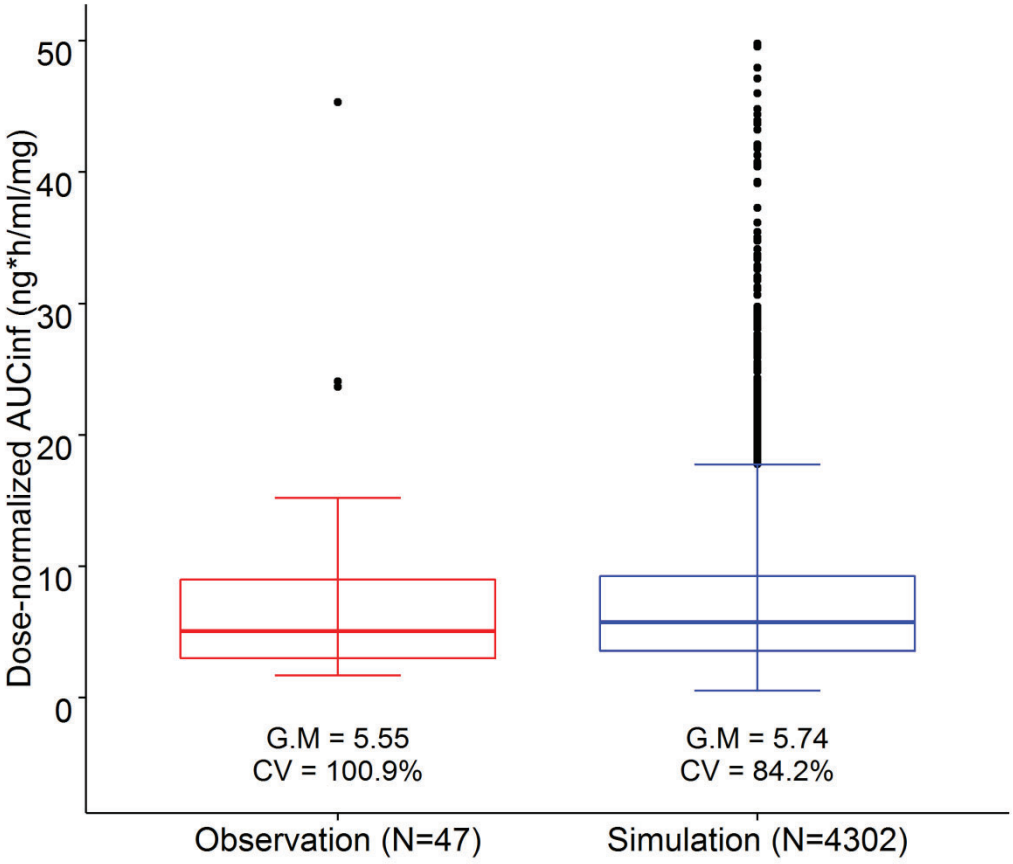
Figure 4. Goodness-of-fit Plots of Dasatinib in Pediatric Patients from Final Pop-PK Model



DV: Observations; PRED: Population Predictions; IPRED: Individual Predictions; CWRES: Conditional Weighted Residuals. IWRES: Individual Weighted Residuals. Blue dots: steady-state concentrations. Red dots: non steady-state concentrations. Red solid line: Loess smooth through data.

Figure 5. Comparison of Dose-normalized AUCinf Based on Observations and Simulations in Pediatric Patients Who Took Intact Tablet in Phase 1 Trial CA180018



G.M: Geometric Mean.
CV: Coefficient of Variation
Note: 52 patients have taken 74 intact tablet administrations in Trial CA180018, AUCinf was evaluable in 47 occasions. 100 replicates of simulations were conducted to predict the dasatinib concentrations in these 74 intact tablet administrations. AUCinf were calculated using non-compartmental analysis. AUCinf was calculated based on IPRED+Residual Error for simulations.

4.3.3 Model Applications

4.3.3.1 Assessment of 60 mg/m^2 tablet

The covariates tested in the full model include covariate effects of baseline bodyweight on clearance (CL) and volume of distribution (VC), and the effect of formulation on absorption rate (KA) and relative bioavailability (FR). Their estimated covariate effects were shown in Figure 2. Weight is a significant covariate on clearance and volume of distribution. The ratio of CL and VC comparing a patient weighing 85 kg to a patient weighing 40 kg was estimated to be 1.4 (95% CI: [1.2, 1.6]) and 1.77 (95% CI: [1.5, 2.2]) (Figure 2).

Simulation was conducted to predict and compare dasatinib exposure of 60 mg/m^2 tablet among pediatric patients in age groups [1,6), [6,12), [12,18) and adult patient population (older than 18 years old). The covariate information (age, body weight and body surface area [BSA]) used in the simulation was resampled randomly from the National Health and Nutrition Examination Survey (2013-2014). Figure 6 presents the distribution of steady-state dasatinib exposure (Cavgss, Ctroughss and Cmaxss) by adults and pediatric patients in 3 age groups. The steady-state dasatinib exposure appeared to increase slightly with age in pediatric patients, with Cavg in age group [1,6) about 16% lower than the age group [6,12).

Dasatinib exposure of 60 mg/m^2 tablet were also simulated and compared among pediatric patients with different weight bands [10kg, 25kg), [25kg, 45kg) and [45 kg,) (Figure 7). Similarly, the steady-state average dasatinib exposure (Cavgss) appeared to increase with body weight in pediatric patients, but the difference in geometric mean between patients in different weight categories is less than 20%.

As shown in both Figure 6 and Figure 7, the Cavg in pediatric patients were comparable to the Cavg in adult patients, but the Ctroughss and Cmaxss in pediatric patients were ~ 42% lower and ~20% higher than that of adult patients at 100 mg flat dose, respectively.

Figure 6. Distribution of Simulated Exposure of 60 mg/m^2 Tablet in Pediatric Patients by Age groups, and 100 mg in Adult Patient

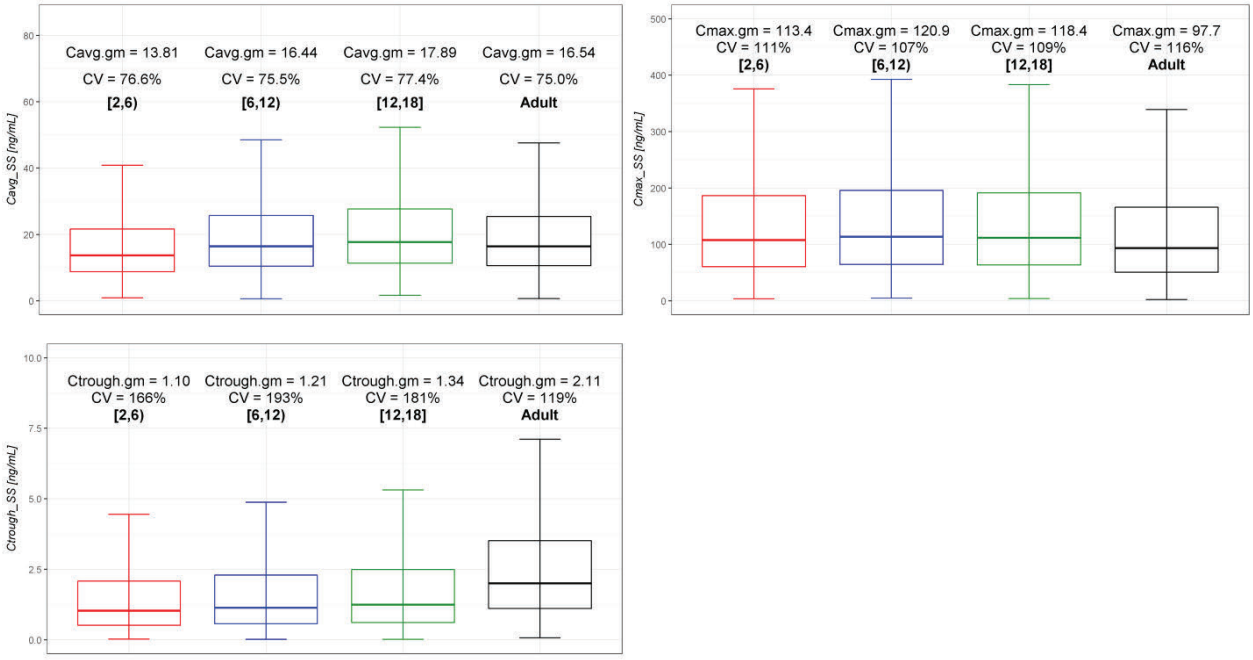


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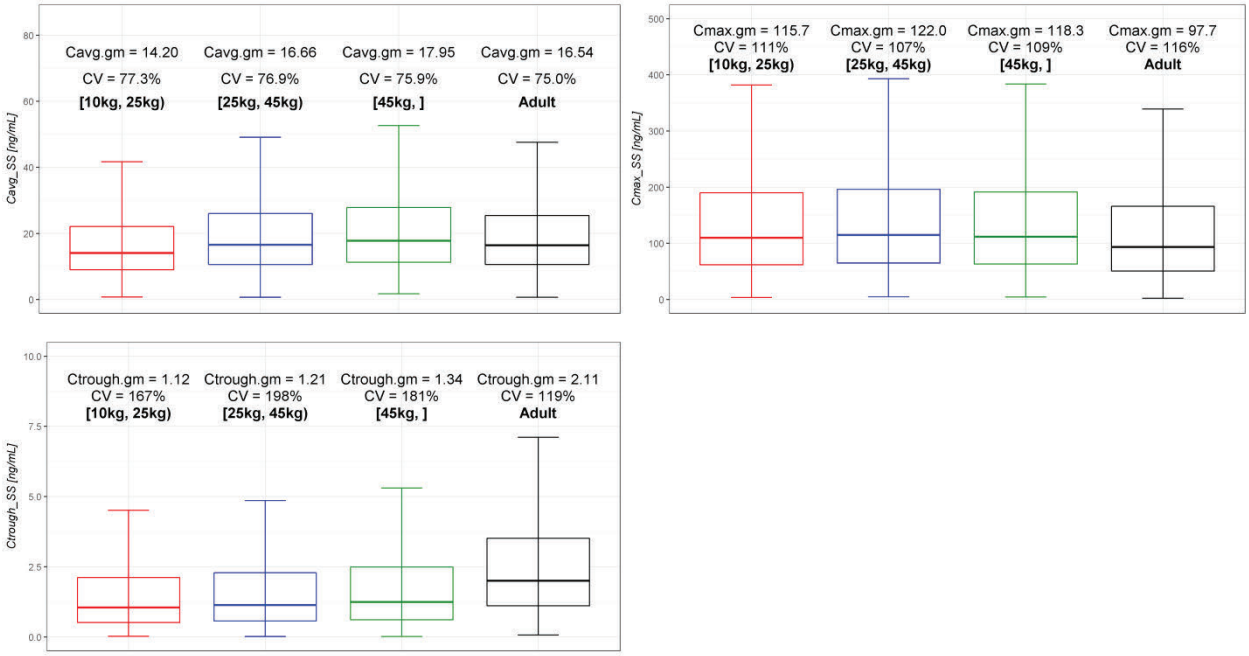
Figure 7. Distribution of Simulated Exposure of 60 mg/m^2 Tablet in Pediatric Patients by Body Weight Categories, and 100 mg in Adult Patient



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4.3.3.2 Determination of WT-Tiered Tablet Doses

Although the body surface area (BSA)-normalized dosing was evaluated through the dasatinib pediatric development program, the actual mg dose in the clinical practice is constrained by the commercially available dasatinib tablet strengths of 20, 50, 70, 80, and 100 mg. Thus a weight (WT)-tiered dosing approach is evaluated for the pediatric tablet. WT-tiered dosing regimen is identified by applying model-based simulation to determine the doses that produce dasatinib exposure similar to target exposure of the 60 mg/m^2 tablet in pediatric patients with Ph+ CML in chronic phase. The exposure of weight-tiered dose is considered similar if the geometric mean of simulated steady-state exposure is within 20% of the target exposure. In addition, the percentage of pediatric patients attaining exposures within the 10th and 90th percentiles of the target exposures were calculated and compared to the nominal value of 80%. Table 8 presents geometric means of the predicted Cavgss at proposed weight-tiered doses (with every 5 mg increment) and at the reference dose of 60 mg/m^2 tablet. The reviewer agrees that the majority of WT-tiered doses proposed by the applicant are expected to provide Cavgss within 20% difference of reference exposure except for the proposed doses at weight category 20 kg to less than 30 kg. As shown in Table 8, a (b) (4) flat dose is expected to produce about 23% lower exposure compared to reference 60 mg/m^2 tablet in pediatric patients weighing between 20 kg to less than 25 kg, whereas a (b) (4) flat dose is expected to produce 18.5% higher exposure compared to the reference tablet in pediatric patients weighing between 25 kg to less than 30 kg. The reviewer is concerned that a 23% lower exposure might compromise the efficacy in these patients considering that patients with lower exposure was found to have a trend of numerically lower rate of MMR based on dose/exposure response analyses. Thus, the agency recommends 60 mg dose for pediatric patients weighing 20 kg to less than 30 kg in the labeling. Simulations showed that a 60 mg dose is expected to produce about 15.5% and 1.6% higher exposure compared to reference 60 mg/m^2 tablet in weight category 20 kg to less than 25 kg and 25 kg to less than 30 kg, respectively.

4.3.3.3 Comparison of Exposure between PFOS and Tablet

The final PPK model was used to simulate dasatinib exposures of various PFOS doses and compare these exposures to the target exposure of tablet 60 mg/m^2. Figure 1 presents the distributions of the predicted dasatinib exposures in terms of Cavgss, Ctroughss and Cmaxss for the tested PFOS dose 72 mg/m^2 in Trial CA1800226, (b) (4) (b) (4) tablet dose 60 mg/m^2.

(b) (4)

4.3 Dose/exposure-response Analyses

4.3.1 Time to Major Molecular Response

Dose-Response of efficacy in pediatric patients with newly diagnosed Ph+ CML in chronic phase was first characterized with respect to time to achieve major molecular response (MMR). The relationship was described by a semi-parametric Cox Proportional-Hazards (CPH) model based on data from 51 patients in Cohort 3a (Tablet 60 mg/m^2) and 33 patients in cohort 3b (PFOS 72 mg/m^2) in CA180026. The full model included effects of treatment cohort, and pre-specified baseline variables (age, body weight and BCR-ABL transcript level). The parameter estimates of full model are listed in Table 10.

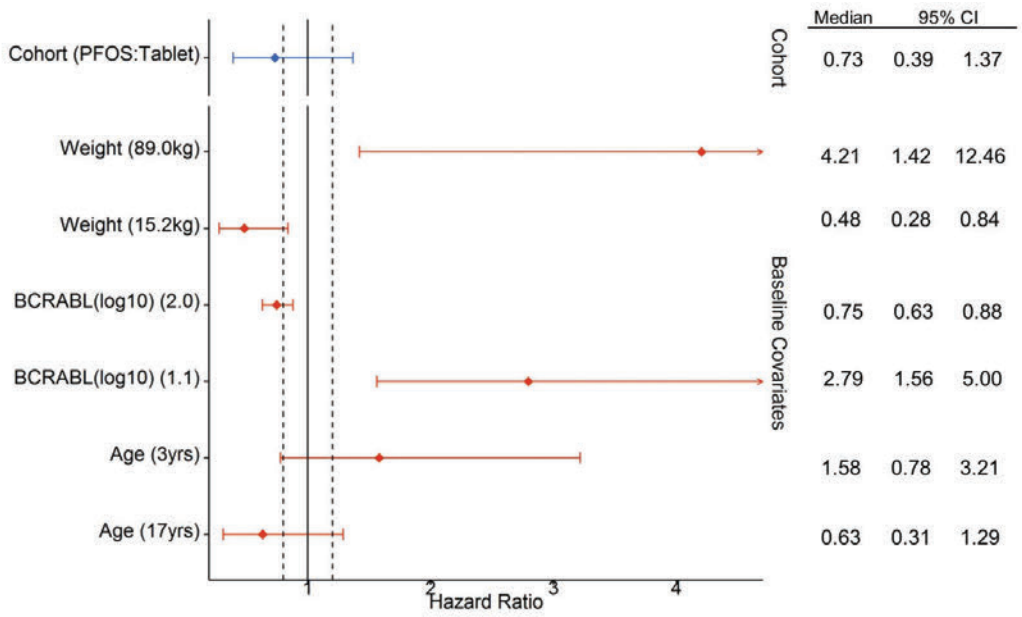
Figure 8 presents a forest plot of all the estimated effects in the full model, showing the hazard ratios comparing extreme values of covariate (5th and 95th) to median value and the associated 95% confidence intervals. The effect of weight and baseline BCR-ABL transcript level were statistically significant covariates on time to MMR. The time to achieve MMR was numerically longer in pediatric patients taking 72 mg/m^2 PFOS (cohort 3b) relative to those taking 60 mg/m^2 Tablet (cohort 3a), although the difference was not statically significant (HR: 0.73 (95% CI: 0.39, 1.37)).

An exposure-response analysis was conducted to evaluate the effect of dasatinib exposure on time to achieve MMR in cohort 3b only as no PK data was collected in cohort 3a. Figure 9 shows the estimated exposure and covariate effects. Consistent with the D-R analysis results, there was a trend of increased MMR probability with increasing dasatinib exposure as measured by Cavgss, although the effect was not statistically significant.

Table 10. Parameter Estimates of D-R (MMR) Full Model

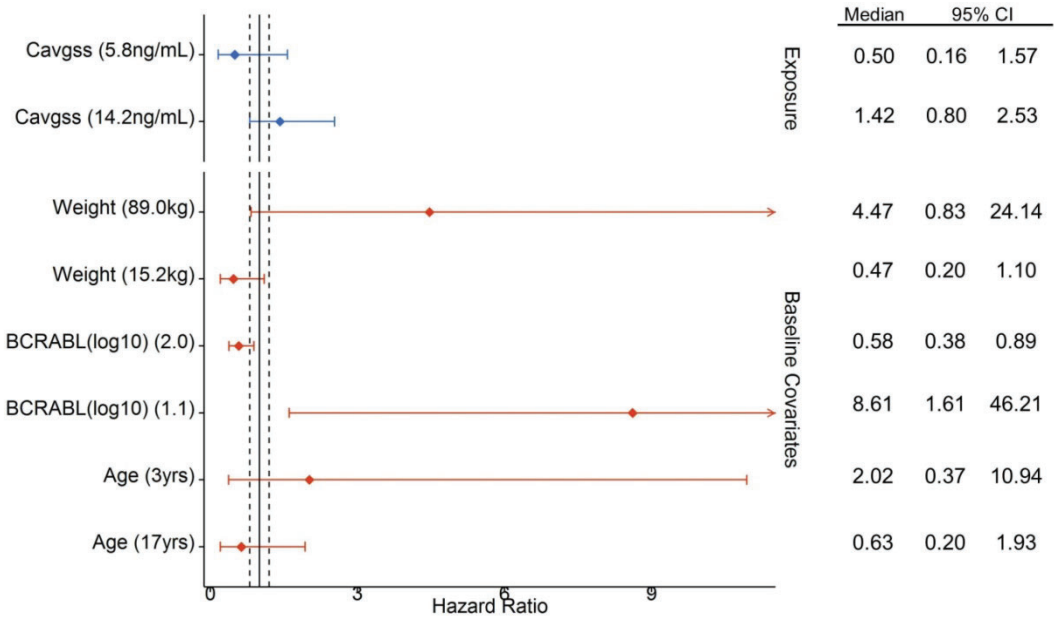
Predictor	Estimate	SE	Hazard Ratio (95% CI)
Cohort (72 mg/m^2 PFOS vs 60 mg/m^2 Tablet)	-0.3124	0.3186	0.73 (0.39, 1.37)
Age (yr)	-0.0654	0.0517	0.94 (0.85, 1.04)
Body Weight (kg)	0.0293	0.0113	1.03 (1.01, 1.05)
Baseline BCR-ABL Transcript Level (Log 10)	-1.4681	0.4245	0.23 (0.10, 0.53)

Figure 8. Estimated Covariate Effects of D-R of MMR (Full Model)



Reference: Age: 12yrs, Weight: 40kg, BCRABL (log10): 1.8

Figure 9. Estimated Covariate Effects of E-R of MMR (Full Model)



Reference: Age: 12yrs, Weight: 40kg, BCRABL (log10): 1.8

4.3.2 BCR-ABL Pharmacodynamics

The longitudinal temporal profiles of BCR-ABL transcript levels in bone marrow cells were evaluated and compared between cohort 3a and cohort 3b as a complement to the dose-response (D-R) analysis of time to achieve MMR. The longitudinal decline of BCR-ABL during dasatinib treatment was best described with a bi-phasic exponential function: log10(BCR-ABL)=log10 (A*exp(-$\alpha * t$)+ B*exp(- $* t$)). 22 patients in cohort 3b who took PFOS 72 mg/m^2 switched to tablet after 1 year, and the BCR-ABL data which were measured after they switched to tablet were excluded by the reviewer from the analysis. The effects of treatment cohort, body weight and age on α were estimated in the full model. The parameter estimates of the full model were shown in Table 11. The performance of the full model was evaluated by diagnostic plots (Figure 10) and visual predictive check stratified by formulation (Figure 11). Both support the validity of the full model to describe the BCR-ABL pharmacodynamics and to provide inferences of covariates effects. The estimated covariates presented in Figure 12 shows the effects of age, weight and cohort were not statistically significant. The initial decline rate of

BCR-ABL transcript levels appeared to be comparable between PFOS 72 mg/m^2 and tablet 60 mg/m^2 (ratio comparing PFOS to tablet: 0.98 with 95% CI of 0.81 to 1.20).

(b) (4)

. Consistent with the D-R analysis, dasatinib Cavg was not a significant predictor of the initial decline rate of BCR-ABL transcript level in pediatric patients. The estimated covariate effects of the sensitivity E-R (Figure 13) analysis showed that the initial decline rate of BCR-ABL were estimated to be very similar across patients with various levels of dasatinib exposure.

Table 11. Parameter Estimates of D-R (BCR-ABL) Full Model

Parameter [Units]	Parameter Estimate	Standard Error (RSE%)	95% Confidence Interval[a]
Fixed Effects			
ALPHA	1.27	0.112 (8.8)	1.05 – 1.46
BETA	0.063	0.01 (15.9)	0.0373 – 0.0887
A	51.4	4.67 (9.1)	42.5 – 59
B	0.186	0.0552 (29.7)	0.107 – 0.288
ALPHAcohort	-0.0257	0.124 (482.5)	-0.206 – 0.183
ALPHAage	-0.0258	0.173 (670.5)	-0.323 – 0.413
ALPHAbwt	0.289	0.239 (82.7)	-0.15 – 0.69
Random Effects[c]			
ω^2beta [-]	0.625 (0.79)	0.2 (32%)	0.313 – 1.19
ω^2beta, B [-]	-0.413	0.462 (111.9%)	-1.37 – 0.549
ω^2B [-]	5 (2.24)	0.973 (19.5%)	3.54 – 6.91
Residual Error			
θLADD [-]	0.58	0.0534 (9.2%)	0.49 – 0.661

a. Confidence intervals were generated based on 500 bootstrap results.

Figure 10. Goodness-of-fit Plots of BCR-ABL Transcript Levels in Pediatric Patients from Final Model

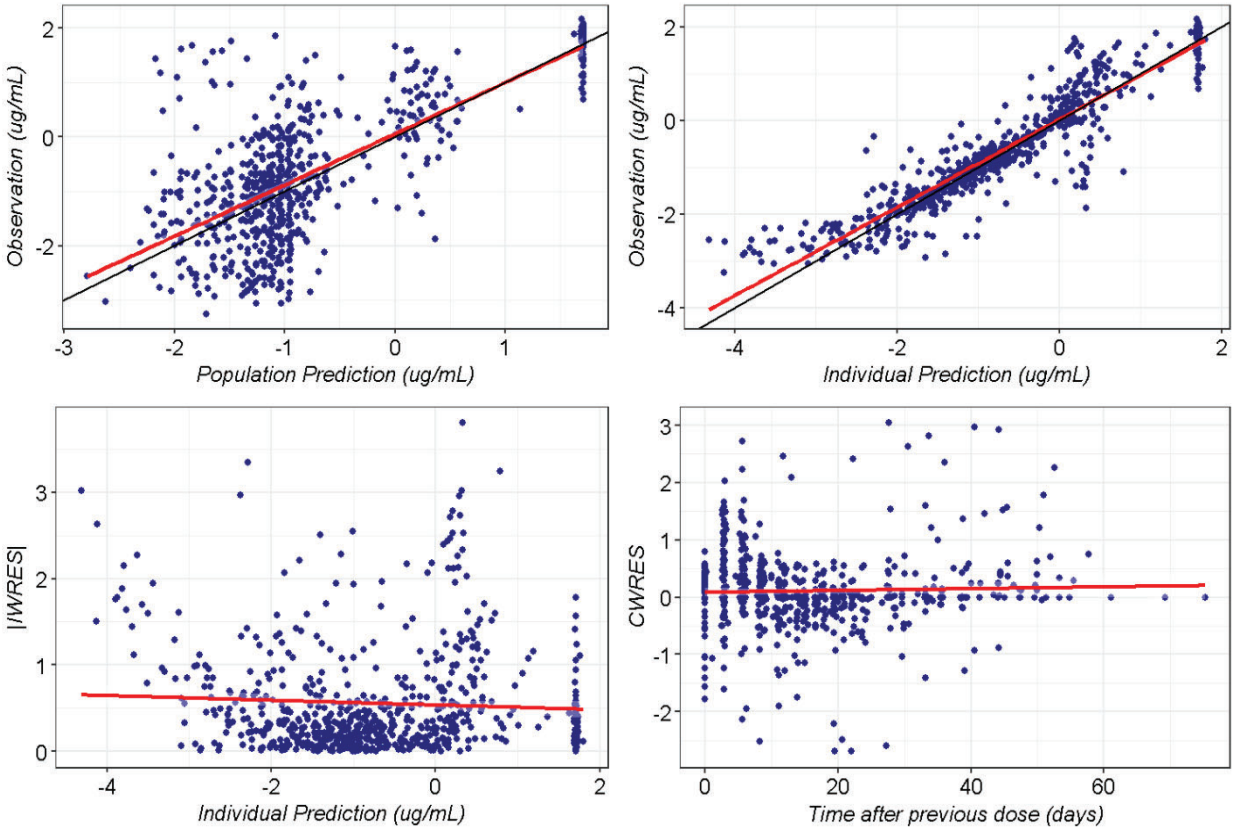


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Figure 11. Visual Predictive Check of BCR-ABL Pharmacodynamics (Full Model)

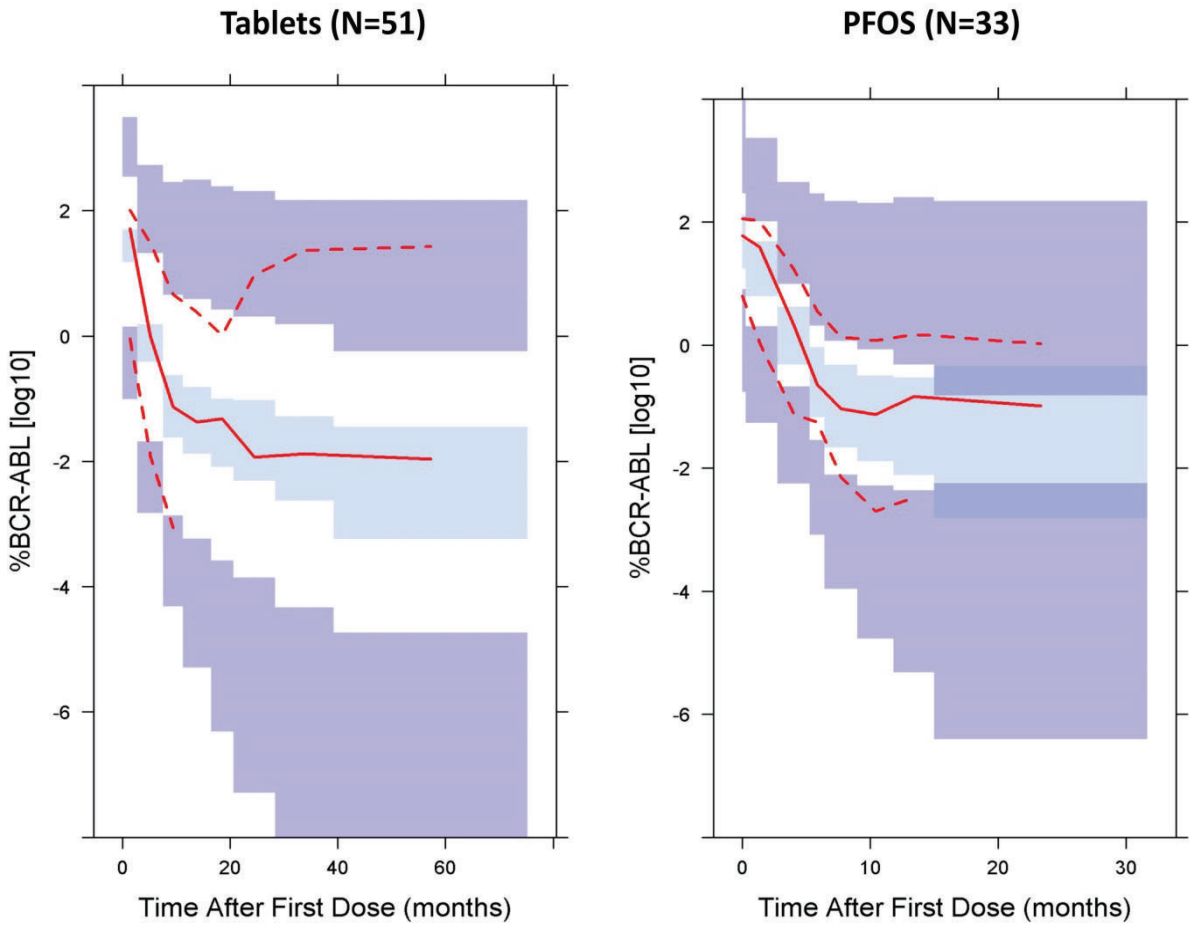

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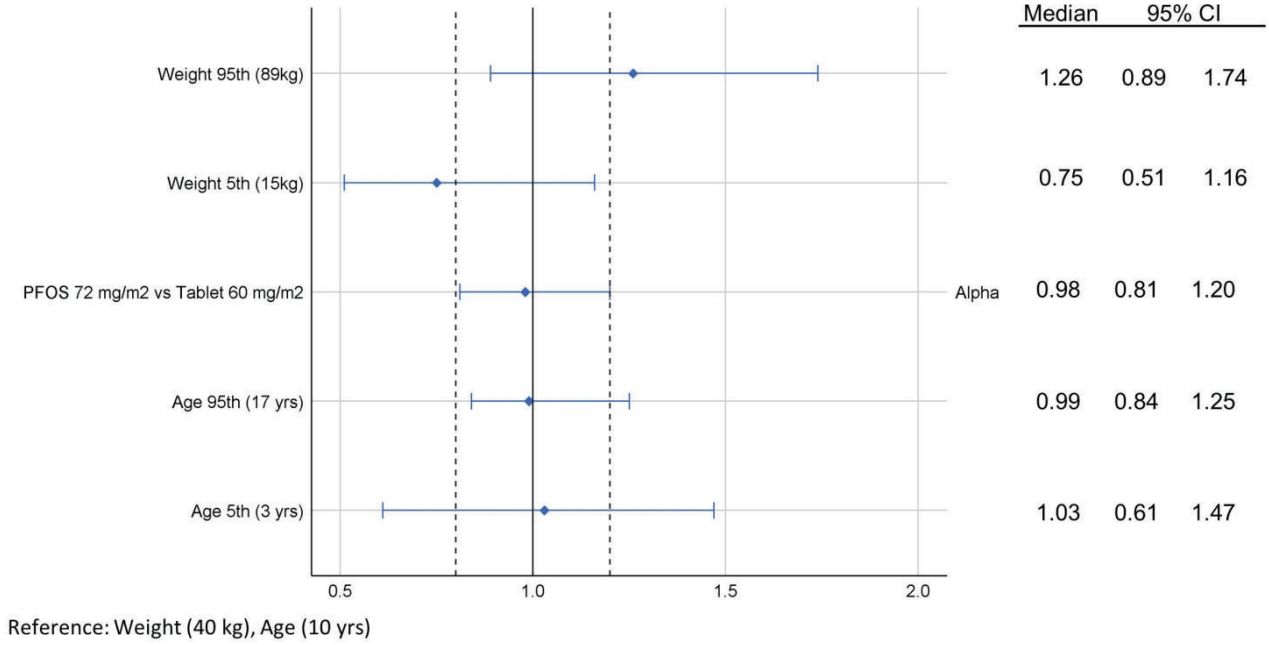
Figure 12. Estimated Covariate Effects of D-R (BCR-ABL Pharmacodynamics) Model



Reference: Weight (40 kg), Age (10 yrs)

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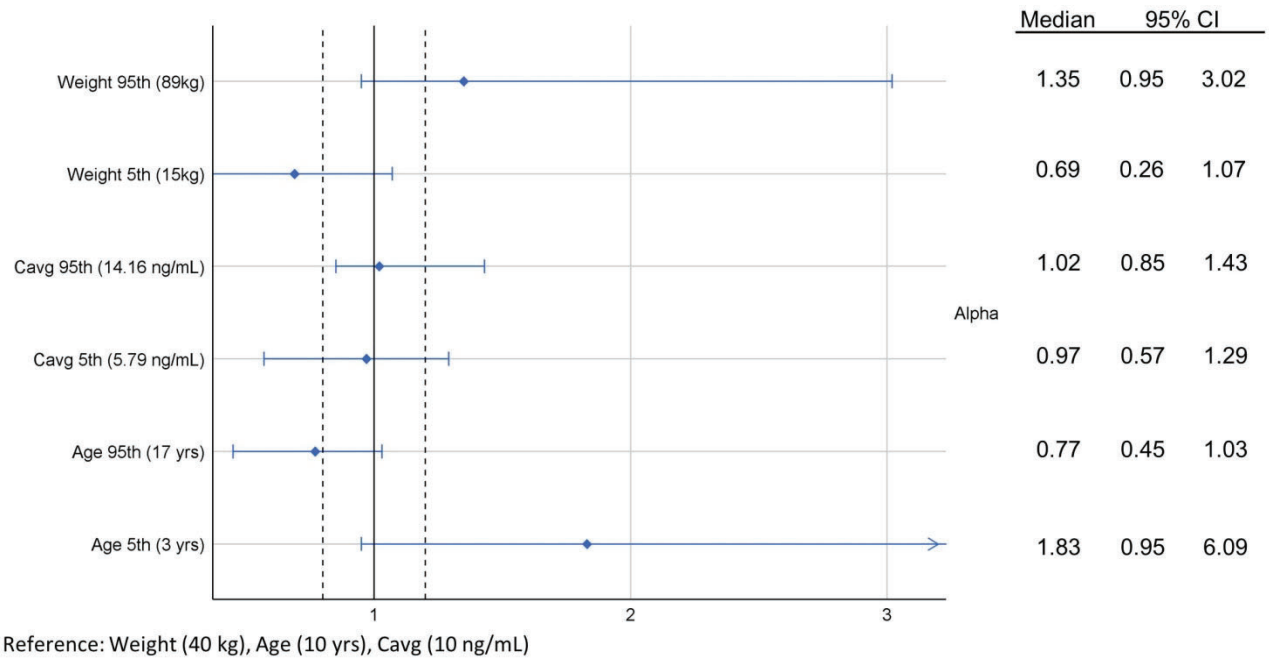
Figure 13. Estimated Covariate Effects of E-R (BCR-ABL Pharmacodynamics) Model



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/s/

YUHONG CHEN
10/06/2017

YOUWEI N BI
10/06/2017

JUSTIN C EARP
10/06/2017

STACY S SHORD
10/06/2017

NAM ATIQUR RAHMAN
10/06/2017
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21986Orig1s020

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 9, 2017
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 21986/ S-020
Product Name and Strength:	Sprycel (dasatinib) film-coated tablets, 20 mg, 50 mg, 70 mg, 80 mg, 100 mg, and 140 mg
Applicant/Sponsor Name:	Bristol-Myers Squibb
Submission Date:	September 27, 2017
OSE RCM #:	2017-906-1
DMEPA Safety Evaluator:	Casmir Ogbonna, PharmD, MBA, BCPS, BCGP
DMEPA Team Leader:	Hina Mehta, PharmD.

1 PURPOSE OF MEMO

The Division of Hematology Products (DHP) requested that we review the revised carton and container labels for Sprycel (dasatinib) tablets (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

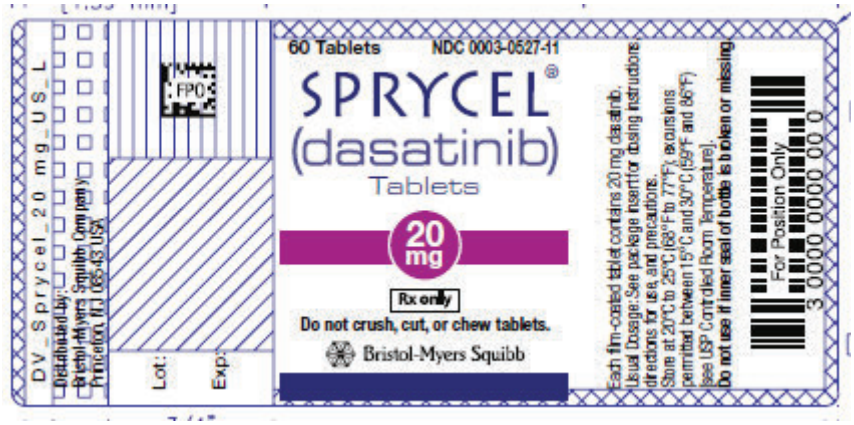
2 CONCLUSION

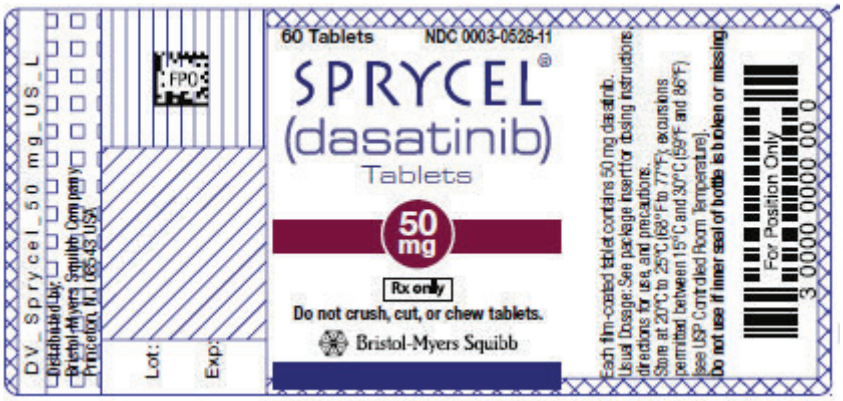
The revised carton and container labels for Sprycel (dasatinib) tablets are acceptable from a medication error perspective. We have no further recommendations at this time.

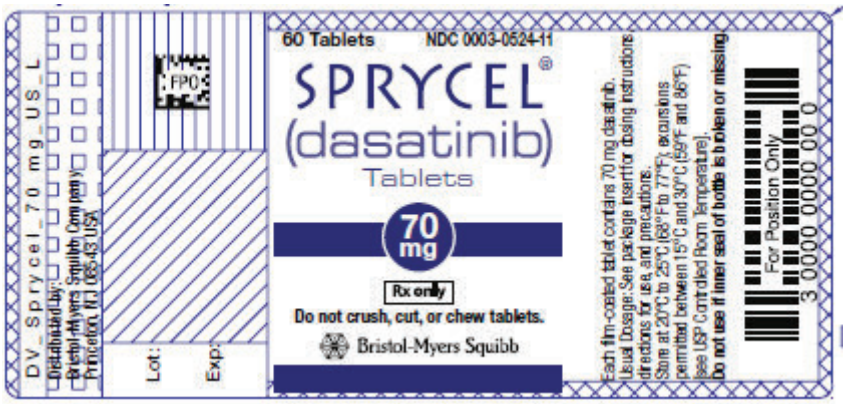
[a] Ogbonna, C. Label and Labeling Review for Sprycel (dasatinib) (NDA 21986/ S-020). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 SEP 12. RCM No.: 2017-907 and 2017-906.

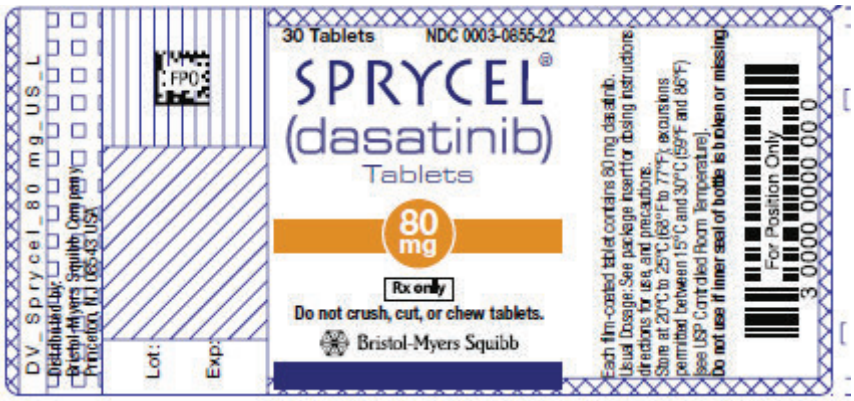
APPENDIX A. LABEL AND LABELING SUBMITTED ON 9/27/2017

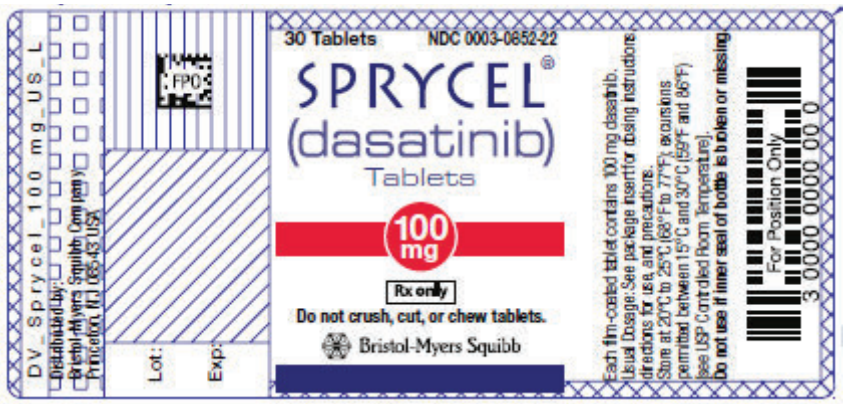
Container labels

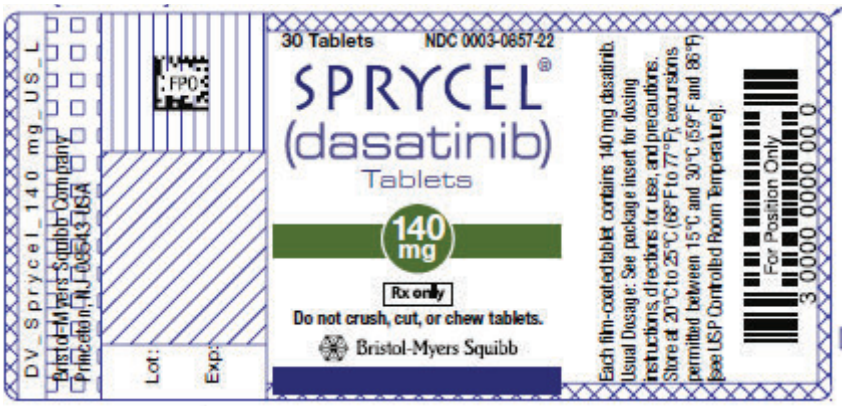




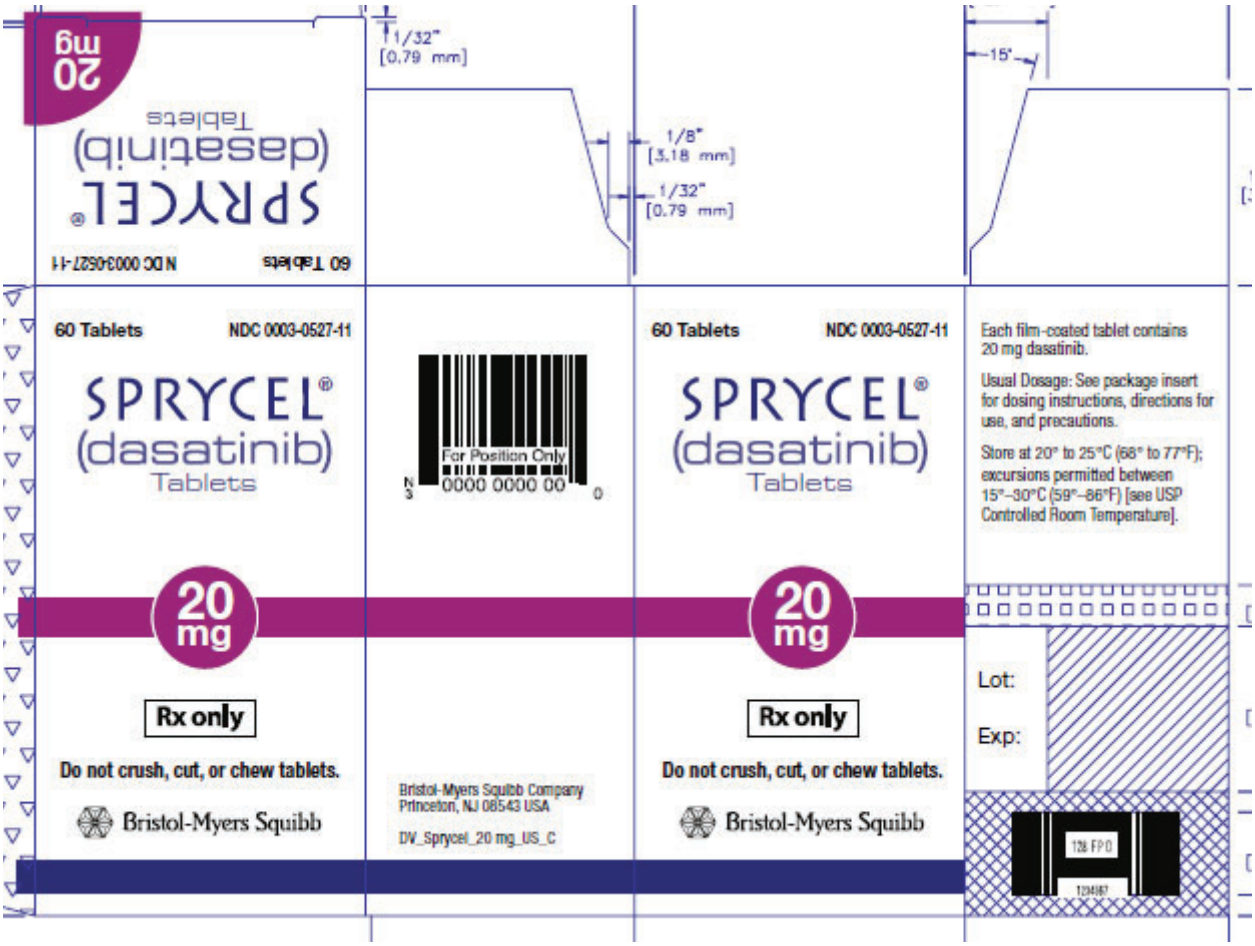


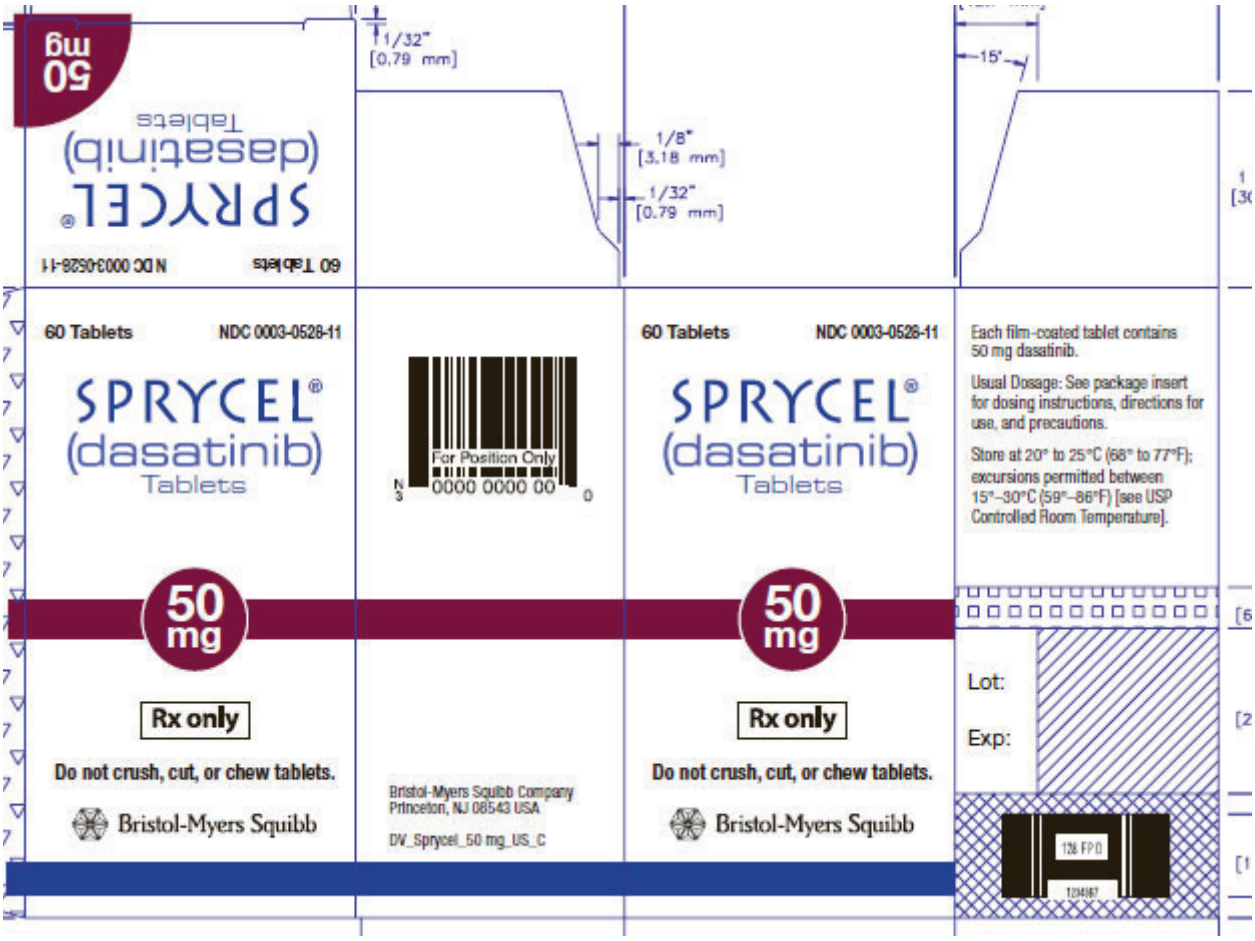


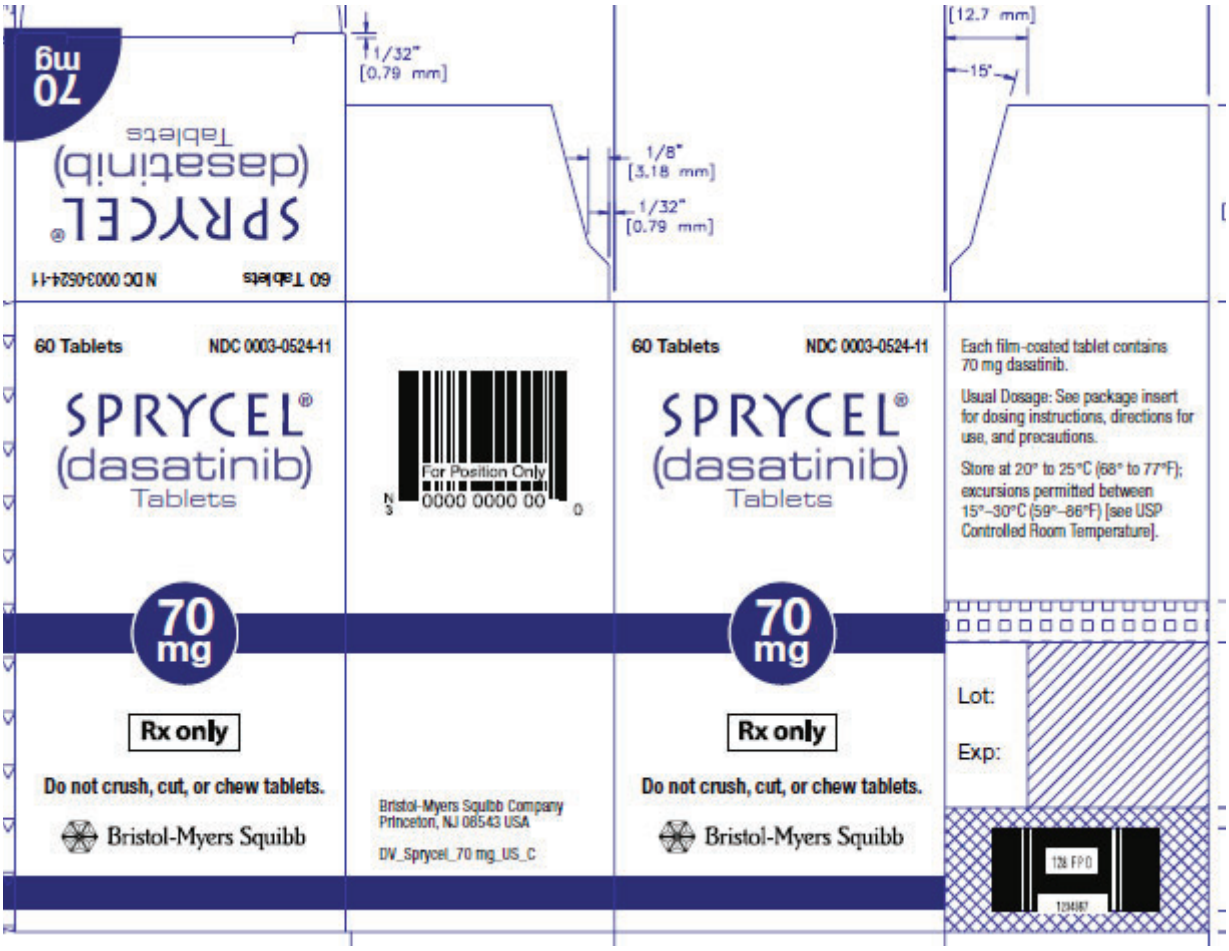


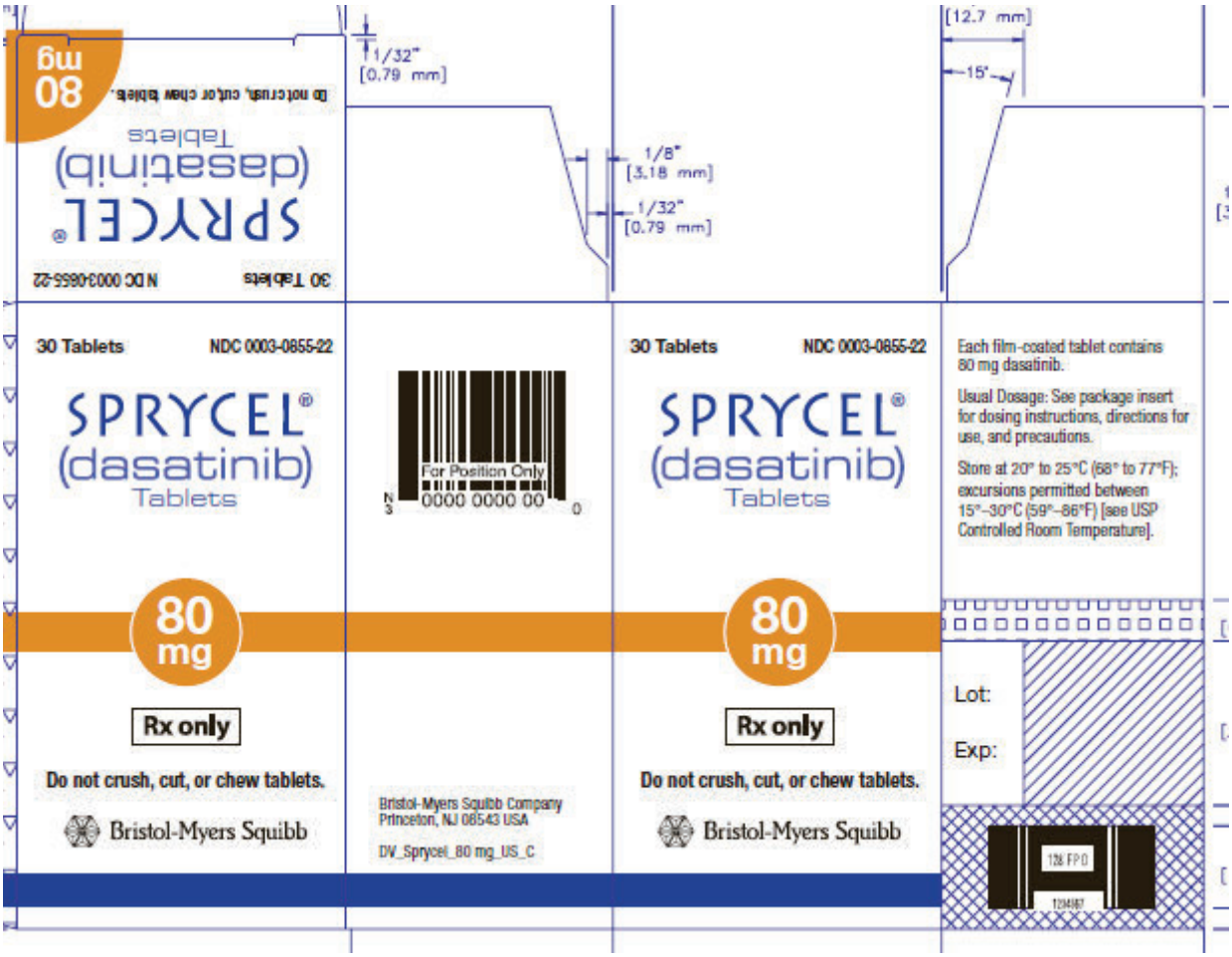


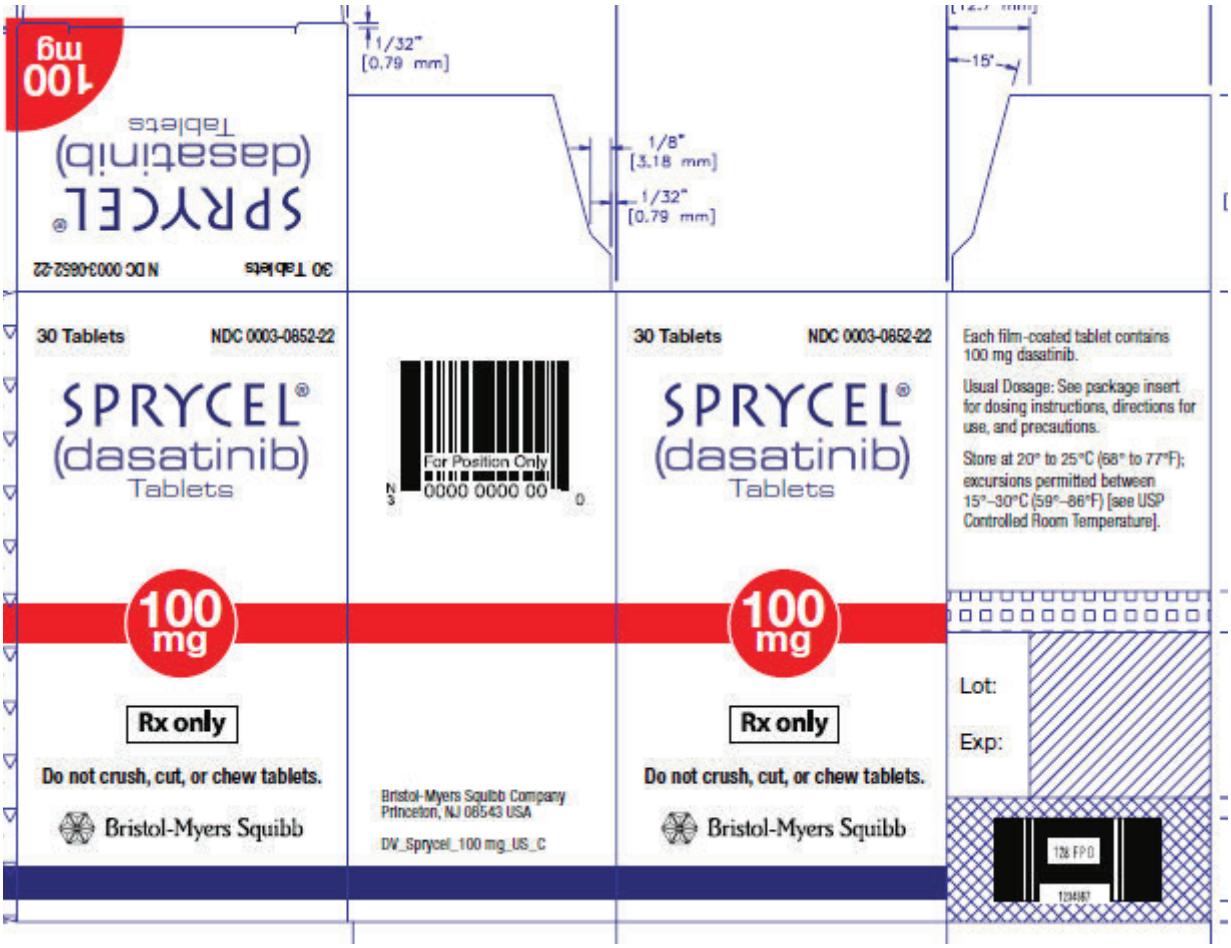
Carton labeling


20 mg
Tablets
(dasatinib)
SPRYCEL®
60 Tablets
NDC 0003-0527-11
1/32"
[0.79 mm]
1/8"
[3.18 mm]
1/32"
[0.79 mm]
15°
60 Tablets
NDC 0003-0527-11
SPRYCEL®
(dasatinib)
Tablets
20 mg
Rx only
Do not crush, cut, or chew tablets.
Bristol-Myers Squibb
For Position Only
0000 0000 00
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA
DV_Sprycel_20 mg_US_C
60 Tablets
NDC 0003-0527-11
SPRYCEL®
(dasatinib)
Tablets
20 mg
Rx only
Do not crush, cut, or chew tablets.
Bristol-Myers Squibb
Each film-coated tablet contains 20 mg dasatinib.
Usual Dosage: See package insert for dosing instructions, directions for use, and precautions.
Store at 20° to 25°C (68° to 77°F); excursions permitted between 15°–30°C (59°–86°F) [see USP Controlled Room Temperature].
Lot:
Exp:
126 FPO
120497


50 mg
SPRYCEL® (dasatinib) Tablets
60 Tablets NDC 0003-0528-11
1/32" [0.79 mm]
1/8" [3.18 mm]
1/32" [0.79 mm]
15°
60 Tablets NDC 0003-0528-11
SPRYCEL® (dasatinib) Tablets
50 mg
Rx only
Do not crush, cut, or chew tablets.
Bristol-Myers Squibb
For Position Only
0000 0000 00
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA
DV_Sprycel_50 mg_US_C
60 Tablets NDC 0003-0528-11
SPRYCEL® (dasatinib) Tablets
50 mg
Rx only
Do not crush, cut, or chew tablets.
Bristol-Myers Squibb
Each film-coated tablet contains 50 mg dasatinib.
Usual Dosage: See package insert for dosing instructions, directions for use, and precautions.
Store at 20° to 25°C (68° to 77°F); excursions permitted between 15°–30°C (59°–86°F) [see USP Controlled Room Temperature].
Lot:
Exp:
12B FPO
1234567


70 mg
SPRYCEL® (dasatinib) Tablets
60 Tablets NDC 0003-0524-11
1/32" [0.79 mm]
1/8" [3.18 mm]
1/32" [0.79 mm]
[12.7 mm]
15°
60 Tablets NDC 0003-0524-11
SPRYCEL®
(dasatinib)
Tablets
70 mg
Rx only
Do not crush, cut, or chew tablets.
Bristol-Myers Squibb
For Position Only
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA
DV_Sprycel_70 mg_US_C
60 Tablets NDC 0003-0524-11
SPRYCEL®
(dasatinib)
Tablets
70 mg
Rx only
Do not crush, cut, or chew tablets.
Bristol-Myers Squibb
Each film-coated tablet contains 70 mg dasatinib.
Usual Dosage: See package insert for dosing instructions, directions for use, and precautions.
Store at 20° to 25°C (68° to 77°F); excursions permitted between 15°–30°C (59°–86°F) [see USP Controlled Room Temperature].
Lot:
Exp:


80 mg
Do not crush, cut, or chew tablets.
SPRYCEL®
(dasatinib)
Tablets
30 Tablets
NDC 0003-0855-22
1/32"
[0.79 mm]
1/8"
[3.18 mm]
1/32"
[0.79 mm]
[12.7 mm]
15°
30 Tablets
NDC 0003-0855-22
SPRYCEL®
(dasatinib)
Tablets
For Position Only
0000 0000 00
80 mg
Rx only
Do not crush, cut, or chew tablets.
Bristol-Myers Squibb
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA
DV_Sprycel_80 mg_US_C
Each film-coated tablet contains 80 mg dasatinib.
Usual Dosage: See package insert for dosing instructions, directions for use, and precautions.
Store at 20° to 25°C (68° to 77°F); excursions permitted between 15°–30°C (59°–86°F) [see USP Controlled Room Temperature].
Lot:
Exp:
80 mg
Rx only
Do not crush, cut, or chew tablets.
Bristol-Myers Squibb


100 mg
SPRYCEL® (dasatinib) Tablets
30 Tablets NDC 0003-0852-22
1/32" [0.79 mm]
1/8" [3.18 mm]
1/32" [0.79 mm]
15°
30 Tablets NDC 0003-0852-22
SPRYCEL® (dasatinib) Tablets
100 mg
Rx only
Do not crush, cut, or chew tablets.
Bristol-Myers Squibb
For Position Only
0000 0000 00
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA
DV_Sprycel_100 mg_US_C
30 Tablets NDC 0003-0852-22
SPRYCEL® (dasatinib) Tablets
100 mg
Rx only
Do not crush, cut, or chew tablets.
Bristol-Myers Squibb
Each film-coated tablet contains 100 mg dasatinib.
Usual Dosage: See package insert for dosing instructions, directions for use, and precautions.
Store at 20° to 25°C (68° to 77°F); excursions permitted between 15°–30°C (59°–86°F) [see USP Controlled Room Temperature].
Lot:
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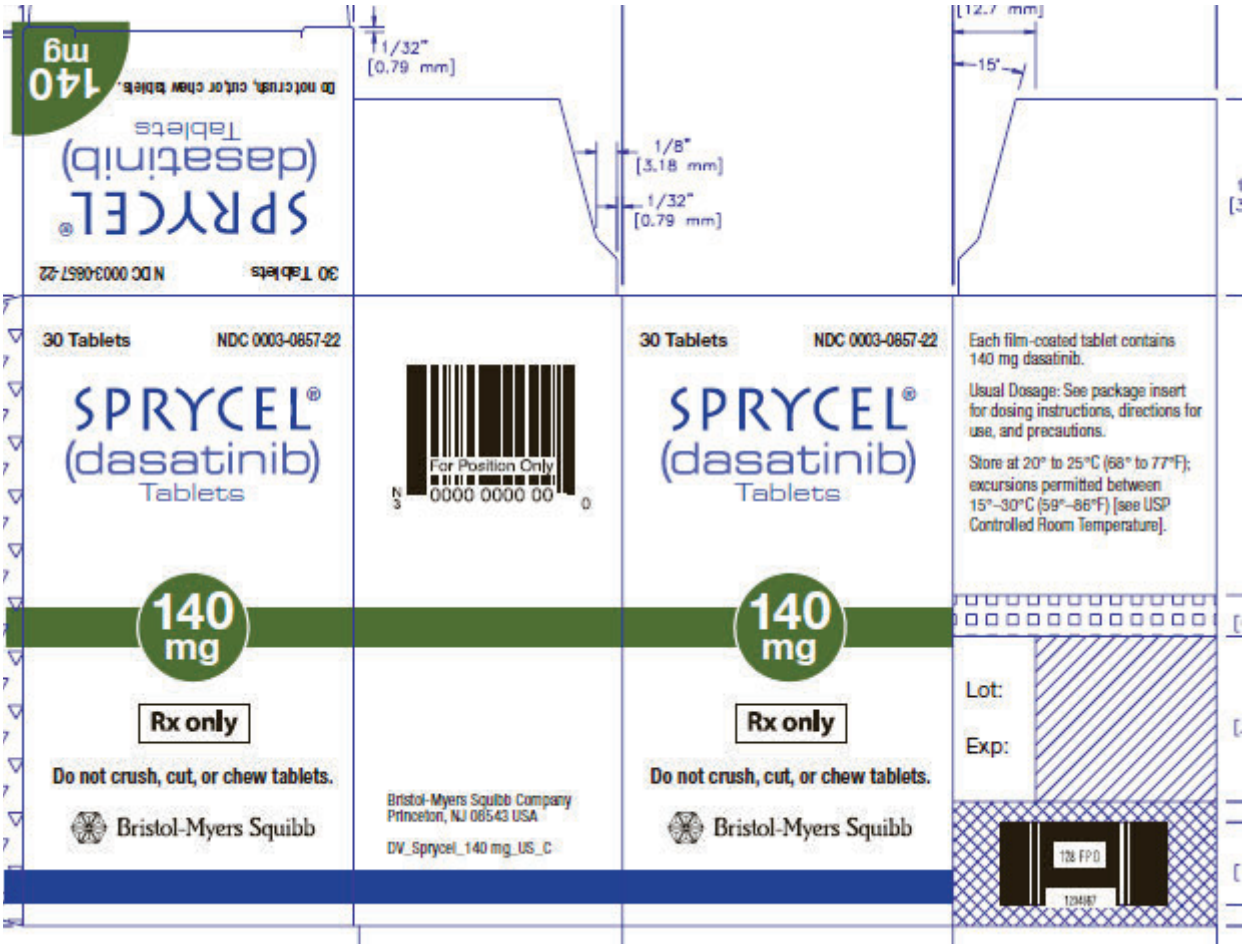
140 mg
Do not crush, cut, or chew tablets.
SPRYCEL®
(dasatinib)
Tablets
30 Tablets
NDC 0003-0857-22
1/32"
[0.79 mm]
1/8"
[3.18 mm]
1/32"
[0.79 mm]
15°
30 Tablets
NDC 0003-0857-22
SPRYCEL®
(dasatinib)
Tablets
For Position Only
0000 0000 00
140 mg
Rx only
Do not crush, cut, or chew tablets.
Bristol-Myers Squibb
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA
DV_Sprycel_140 mg_US_C
30 Tablets
NDC 0003-0857-22
SPRYCEL®
(dasatinib)
Tablets
140 mg
Rx only
Do not crush, cut, or chew tablets.
Bristol-Myers Squibb
Each film-coated tablet contains 140 mg dasatinib.
Usual Dosage: See package insert for dosing instructions, directions for use, and precautions.
Store at 20° to 25°C (68° to 77°F); excursions permitted between 15°–30°C (59°–86°F) [see USP Controlled Room Temperature].
Lot:
Exp:
128 FPO
123457

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/s/

CASMIR I OGBONNA
11/09/2017

HINA S MEHTA
11/09/2017

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	October 2, 2017
To:	Ann Farrell, MD Director **Division of Hematology Products (DHP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Ruth Lidoshore, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rachael Conklin, MS, RN Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	SPRYCEL (dasatinib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 021986
Supplement Number:	S-020
Applicant:	Bristol-Myers Squibb

1 INTRODUCTION

On May 9, 2017, Bristol-Myers Squibb submitted for the Agency's review a Prior Approval Supplement (PAS) – Efficacy to their approved New Drug Application (NDA) 021986/S-020 for SPRYCEL (dasatinib) tablets. In this efficacy supplement, the Applicant seeks an additional indication for use in pediatric patients with Philadelphia chromosome positive (Ph+) chronic phase chronic myeloid leukemia (CP-CML).

SPRYCEL (dasatinib) tablets was originally approved on June 28, 2006 and is indicated for

- newly diagnosed adults with Ph+ CP-CML
- adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib
- adults with Ph+ acute lymphoblastic leukemia with resistance or intolerance to prior therapy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on June 9, 2017, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for SPRYCEL (dasatinib) tablets.

2 MATERIAL REVIEWED

- Draft SPRYCEL (dasatinib) PPI received on August 23, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 20, 2017.
- Draft SPRYCEL (dasatinib) Prescribing Information (PI) received on August 23, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 20, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

RUTH I LIDOSHORE
10/02/2017

RACHAEL E CONKLIN
10/02/2017

BARBARA A FULLER
10/03/2017

LASHAWN M GRIFFITHS
10/03/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 10/2/17

To: Wan Lee, Regulatory Project Manager
Division of Hematology Products (DHP)

Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Rachael Conklin, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Nisha Patel, Acting Team Leader, OPDP

Subject: OPDP Labeling Comments for SPRYCEL (dasatinib) tablets, for oral use

NDA: 021986/S-020

In response to DHP's consult request dated June 9, 2017, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for SPRYCEL (dasatanib) tablets, for oral use (Sprycel). This supplement (S-20) provides for use in pediatric patients with Philadelphia chromosome-positive chronic myeloid leukemia (CML) in the chronic phase.

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI emailed to OPDP on September 20, 2017, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling emailed to OPDP on September 20, 2017, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Rachael Conklin at 240-402-8189 or rachael.conklin@fda.hhs.gov.

PI

Section	Statement from Draft (if applicable)	OPDP Comment
HIGHLIGHTS OF PRESCRIBING INFORMATION: ADVERSE REACTIONS	(b) (4)	OPDP notes that (b) (4) (b) (4) Table 10 "Adverse Reactions Reported in ≥10% of Adult Patients with Advanced Phase CML Resistant or Intolerant to Prior Imatinib Therapy" lists (b) (4) (b) (4) OPDP recommends revising this section to include "hemorrhage."
2.3 Dose Modification	**Strong CYP3A4 Inhibitors**	OPDP notes that specific dose modifications are given for the doses used in adult patients. Are there any specific dose reduction guidelines for pediatric patients (noting that pediatric dosing is based on body weight)? If so, OPDP suggests including this information as it may be informative for providers.
5.2 Bleeding-Related Events		OPDP recommends revising this section so that the first sentence clearly states that Sprycel can cause this adverse reaction. As it is currently written this section may distance the product from the risk. E.g., "Sprycel can cause serious or fatal bleeding-related events."
5.4 Cardiovascular Events		Similar to our above comment, OPDP recommends revising this section so that the first sentence clearly states that Sprycel can cause this adverse reaction. As it is currently written this section may distance the product from the risk. E.g., "Sprycel can cause cardiac dysfunction."
6.1 Chronic Myeloid Leukemia (CML)	(b) (4) (b) (4)	Does this information pertain pediatric patients? If not, OPDP suggest revising to clarify the patient population. E.g., "permanent discontinuation of treatment occurred in 2% of patients in a randomized trial of **adult** patients with newly diagnosed chronic phase CML and 5% of **adult** patients with resistance or intolerance to prior imatinib therapy." "Among chronic phase **adult** CML patients with resistance or intolerance . . ." Additionally, OPDP notes that there may be other instances throughout the label where the patient population is not clearly specified and we suggest

	(b) (4)	revising to clarify whether adult or pediatric patients (or both) are being discussed.
17 Patient Counseling Information		Information from sections 5.5, 5.8, and 5.10 should be included here as they contain important risk information on which patients should be counseled. Additionally, information from section 7.2 about the use of antacids should be included in this section.

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/s/

RACHAEL E CONKLIN
10/02/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	September 12, 2017
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	(b) (4) NDA 21986/S-020
Product Name and Strength:	(b) (4) Sprycel (dasatinib) tablets 20 mg, 50 mg, 70 mg, 80 mg, 100 mg, and 140 mg
Product Type:	(b) (4) Single Ingredient (NDA 21986/S-020)
Rx or OTC:	Rx
Applicant/Sponsor Name:	Bristol-Myers Squibb
Submission Date:	May 9, 2017 and August 23, 2017
OSE RCM #:	2017-907 and 2017-906
DMEPA Primary Reviewer:	Casmir Ogbonna, PharmD, MBA, BCPS, BCGP
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

The Division of Hematology Products (DHP) requested that we review the Prescribing Information, Instructions for Use, and carton and container (b) (4) (b) (4) Sprycel (dasatinib) efficacy supplement NDA 21986/S-020, (b) (4) acceptable from a medication error perspective.

1.1 REGULATORY HISTORY

Sprycel (dasatinib) tablets NDA 22070 was approved on June 28, 2006, for the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib. Sprycel is also indicated for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia with resistance or intolerance to prior therapy.

(b) (4)
(b) (4)
(b) (4) an efficacy supplement NDA 21986/S-020 for Sprycel® (dasatinib) tablets for use in pediatric patients with Philadelphia chromosome positive (Ph+) Chronic Phase Chronic Myeloid Leukemia (CP-CML).

(b) (4)
(b) (4) The Sponsor proposed (b) (4) labeling for Sprycel (dasatinib) tablets (NDA 21986). Therefore, the efficacy supplement for NDA 21986/S-020 seeking the new indication in pediatric patients (b) (4)

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
(b) (4)	
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA evaluated the proposed Prescribing Information (PI), Instructions for Use (IFU), container label, and carton labeling for areas of vulnerability in regards to medication error. We note the Instructions for Use are included at the end of the Patient Information sheet. The IFU should be a separate stand-alone document thus we recommend it be separated from the Patient Information Sheet.

We identified areas of concern in the PI in addition to the Sprycel carton and container labeling (b) (4) the tablet formulation that should be revised to improve the clarity of the information presented.

We provide recommendations for the Division in Section 4.1 and for the Applicant in Section 4.2 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

DMEPA identified areas in the labels and labeling that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the PI and 4.2 for the carton and container labels to address these deficiencies.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. HIGHLIGHTS OF PRESCRIBING INFORMATION:

- **Dosage and Administration section**

1. Update the 4th bullet point (b) (4) to include (b) (4) (b) (4) Consider "Do not crush, cut, or chew tablets." This will provide adequate clarity to end users and prevent errors due to possible chewing of tablets.
2. Add a statement to alert the healthcare provider that additional important information is in the Full PI (b) (4)

- **Dosage Forms and Strengths**

(b) (4)

B. DOSAGE AND ADMINISTRATION

1. Section 2: Dosing and Administration, Subsection 2.1, and 2.2

- Update the sentence (b) (4) in both sections to "Tablets should not be crushed, cut, or chewed"…. This will provide adequate clarity to end users and prevent errors due to possible chewing of tablets.
- Replace (b) (4) in the second sentence of section 2.2 with "Sprycel" to be consistent with the rest of the PI.

(b) (4)

4.2 RECOMMENDATIONS FOR BRISTOL-MYERS SQUIBB.

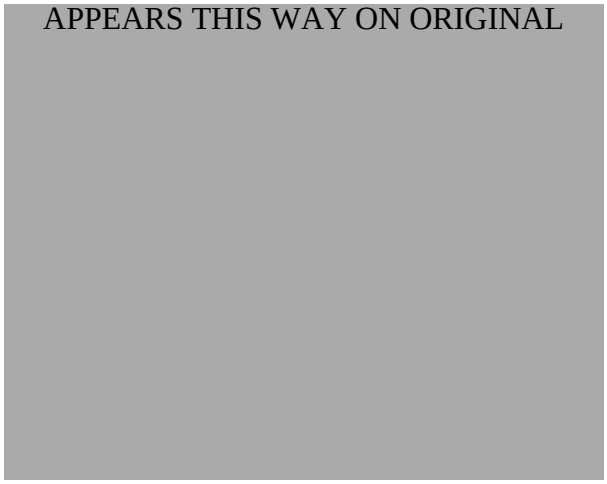
(b) (4)

(b) (4)

C. CONTAINER LABEL FOR SPRYCEL TABLETS (ALL STRENGTHS)

We recommend the following revision be implemented prior to the approval of NDA 21986/S-020.

1. We note that container labels for Sprycel tablets were not submitted for this supplement. However, given that the proposed indication is for pediatrics we recommend you update the statement [redacted] (b) (4) in the Principal Display Panel (PDP) to include [redacted] (b) (4) Revise to "Do not crush, cut, or chew tablets. This will provide adequate clarity to end users and prevent errors due to possible chewing of tablets.



APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Sprycel (dasatinib) that Bristol-Myers Squibb submitted on May 9, 2017.

Table 2. Relevant Product Information for Sprycel	
Initial Approval Date	June 28, 2006
Active Ingredient	dasatinib
Indication	**Adults:** • newly diagnosed adults with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. • adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib. • adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy. **Pediatric:** • pediatric patients with Ph+ CML in chronic phase
Route of Administration	oral
Dosage Form	Tablets (b) (4)
Strength	**Tablets:** 20 mg, 50 mg, 70 mg, 80 mg, 100 mg, and 140 mg (b) (4)
Dose and Frequency	**Adults:** • Chronic phase CML: 100 mg once daily. • Accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL: 140 mg once daily. **Pediatrics:** • Chronic phase CLM: Tablets (b) (4) once daily, starting dose is based on body weight. **Table 1: Dosage of SPRYCEL Tablets for Pediatric Patients** **Body Weight (kg)**[a] **Daily Dose (mg)** (b) (4)

	[redacted] (b) (4) at least 45 kg 100 mg [redacted] (b) (4)
How Supplied	**Tablets:** **20 mg tablet:** NDC 0003-0527-11, white to off-white, biconvex, round, film-coated tablet with “BMS” debossed on one side and “527” on the other side. Contains 60 tablets per bottle. **50 mg tablet:** NDA 0003-0528-11, white to off-white, biconvex, oval, film-coated tablet with “BMS” debossed on one side and “528” on the other side. Contains 60 tablets per bottle. **70 mg tablet:** NDA 0003-0524-11, white to off-white, biconvex, oval, film-coated tablet with “BMS” debossed on one side and “524” on the other side. Contains 60 tablets per bottle. **80 mg tablet:** NDA 0003-0855-22, white to off-white, biconvex, triangle, film-coated tablet with “BMS” and “80” (BMS over 80) debossed on one side and “855” on the other side. Contains 30 tablets per bottle. **100 mg tablet:** NDA 0003-0852-22, white to off-white, biconvex, triangle, film-coated tablet with “BMS” and “100” debossed on one side and “852” on the other side. Contains 30 tablets per bottle. **140 mg tablet:** NDA 0003-0857-22, white to off-white, biconvex, round, film-coated tablet with “BMS” and “140” (BMS over 140) debossed on one side and “857” on the other side. Contains 30 tablets per bottle [redacted] (b) (4)

	(b) (4)
Storage	Sprycel tablets should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. (b) (4)

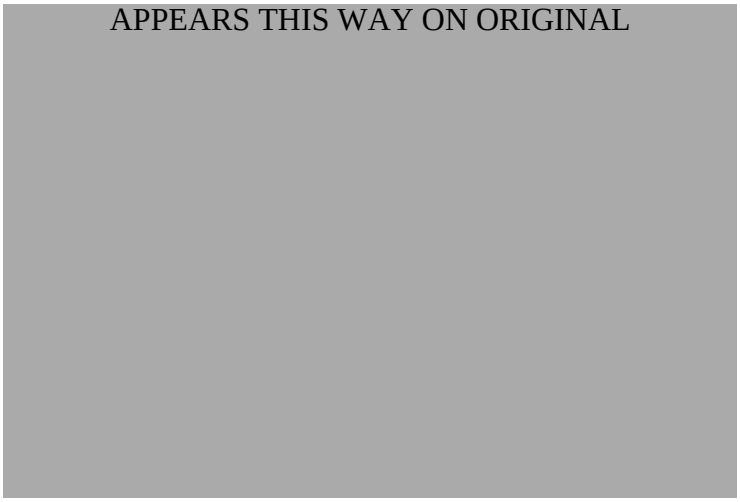
APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On June 14, 2017, we searched the L:drive and AIMS using the terms, Sprycel to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified two previous reviews,[a,b] and we confirmed that our previous recommendations were implemented or considered.



[a] Merchant, L. Label and Labeling Review for Sprycel NDA 21989/S-007. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2010 AUG 13. RCM No.: 2010-1348.

[b] Bridges, T. Proprietary Name Review Memo for Sprycel NDA 21986. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2006 MAY 12. RCM No.: 2006-0124.

APPENDIX D. ISMP NEWSLETTERS

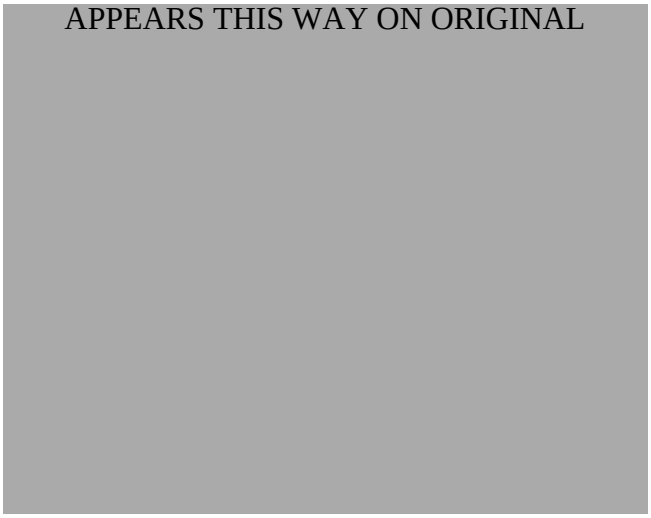
D.1 Methods

On June 14, 2017, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community and Nursing
Search Strategy and Terms	Boolean Query: Sprycel OR dasatinib

D.2 Results

Our search did not identify any relevant reports.



APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Sprycel labels and labeling submitted by Bristol-Myers Squibb on May 9, 2017.

- Container label
- Carton labeling
- Prescribing Information
  \\cdsesub1\evsprod\nda021986\0132\m1\us\pediatric-os-pas-dasat-pro.pdf

APPEARS THIS WAY ON ORIGINAL

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

CASMIR I OGBONNA
09/12/2017

HINA S MEHTA
09/13/2017

CLINICAL INSPECTION SUMMARY

Date	September 13, 2017
From	Anthony Orencia M.D., F.A.C.P., GCPAB Medical Officer Janice Pohlman M.D., M.P.H., GCPAB Team Leader Kassa Ayalew, M.D., M.P.H., GCPAB Branch Chief Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Rachel Ershler, M.D., Medical Officer Nicole Gormley, M.D., Clinical Team Leader Wan Lee, Pharm.D., Regulatory Project Manager Division of Hematology Products
NDA	(b) (4) and NDA 021986 S-020 (tablet)
Applicant	Bristol-Myers Squibb Company
Drug	dasatinib (Sprycel®)
NME	No
Therapeutic Classification/Status	*Src/bcr-abl* tyrosine kinase inhibitor
Proposed Indication	Pediatric Ph+ CML in chronic phase
Consultation Request Date	May 24, 2017
Summary Goal Date	September 1, 2017 (original) September 30, 2017 (extension)
Action Goal Date	November 9, 2017
PDUFA Date	November 9, 2017 [Priority review]

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites (Drs. Gore and Cardos) were selected by the Division of Hematology Products (DHP) for inspection of Study CA180226 submitted in support of NDA 021986 S-020. The study data derived from these clinical sites is considered to be reliable in support of the requested indication.

The final regulatory classification for inspection of Dr. Gore is No Action Indicated (NAI). The preliminary regulatory classification for inspection of Dr. Cardos is Voluntary Action Indicated (VAI).

2. BACKGROUND

Dasatinib is a tyrosine kinase inhibitor of the "BCR-ABL", and "SRC" families. To date, there are no established dasatinib pediatric treatment regimens with Philadelphia chromosome-positive (Ph+), chronic myeloid leukemia (CML) in the chronic phase (CP), who relapsed after, or were resistant or intolerant to imatinib.

The two clinical sites selected for inspection of Study CA180226 submitted in support of this (b) (4) (b) (4) sNDA (tablet) indication were chosen since these may have an impact on the DHP's safety review, as applied to a pediatric or younger population subset.

Study CA180226

Study CA180226 is a Phase 2, open-label, non-randomized, multi-center trial involving subjects with newly diagnosed CML who were treatment-naive and subjects with chronic phase –chronic myeloid leukemia (CP-CML), Ph+ acute lymphoblastic leukemia (ALL) or with Accelerated Phase (AP)-chronic myeloid leukemia (CML) or Blast Phase (BP) chronic myeloid leukemia (CML), who relapsed after, or were resistant or intolerant to, imatinib. It included three cohorts of subjects who received dasatinib orally on a once-daily schedule until disease progression, intolerable toxicity, or subject/physician preference.

Male and female subjects < 18 years of age are enrolled in parallel in the three following cohorts:

- Cohort #1: Children and adolescents with Chronic Phase-CML, who prove resistant or intolerant to imatinib.
- Cohort #2: Children and adolescents with Ph+ ALL, Accelerated Phase-CML or Blast Phase-CML who are resistant or intolerant to, or relapsed after imatinib therapy.
- Cohort #3: Children and adolescents with Chronic Phase-CML, who are treatment-naive (except hydroxyurea).

The primary study objectives are (1) To estimate the major cytogenetic response (MCyR) rate to dasatinib therapy in children and adolescents with Chronic Phase-CML who proved resistant to or intolerant to imatinib (Cohort 1), defined as complete (0%) or partial (1-35% of Ph+ metaphases in at least 20 metaphases in bone marrow), (2) To estimate the complete hematologic response (CHR) rate in children and adolescents with Ph+ ALL, Accelerated Phase-CML and Blast Phase CML, who were resistant to, intolerant to, or who relapsed after prior imatinib therapy (Cohort 2), defined as no more than 5% blasts in bone marrow and normal white blood cell count without blasts in peripheral blood, and (3) To estimate the complete cytogenetic response (CCyR) rate to dasatinib therapy in children and adolescents with newly diagnosed Chronic Phase-CML who are treatment naïve (except hydroxyurea), (Cohort 3).

The primary endpoints are major cytogenetic response (MCyR) for Cohort 1, complete hematologic response (CHR) for Cohort 2, and complete cytogenetic response (CCyR) for Cohort 3. Cytogenetic response criteria are based on the percentage of Ph+ metaphases among 20 analyzed metaphases in bone marrow aspirate. CHR is assessed regularly through hematology tests. Molecular responses are also assessed. Mutation analyses are reported descriptively.

The safety endpoints are adverse events graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

This multicenter study is being conducted at 80 sites worldwide in 18 countries. A total of 145 subjects are enrolled and 130 subjects have been treated with dasatinib. The first subject first visit was March 20, 2009 and the clinical data had a database lock cutoff date of November 4, 2016. Per the Sponsor's overview of the study results, major cytogenetic response (MCyR) for Cohort 1 was achieved in 89.7% of 29 subjects with chronic phase CML, complete hematologic response (CHR) for Cohort 2 was achieved in 29.4% of 17 subjects with advanced disease, and complete cytogenetic response (CCyR) for Cohort 3 was achieved in 94% of 84 subjects with treatment-naïve chronic phase CML.

3. RESULTS (by site):

Name of Clinical Investigator/Sponsor Address	Protocol #/ Site #/# Subjects	Inspection Dates	Classification
Lia Gore, MD Children's Hospital 13123 E 16th Ave Aurora, CO 80045	Protocol CA180226 Site (b) (4) (b) (4) subjects	July 24 to 28, 2017	NAI
Rocio Cardenas Cardos, MD Instituto National De Pediatria Insurgentes Sur 3700 Mexico, Distrito Federal Mexico 04530	Protocol CA180226 Site (b) (4) (b) (4) subjects	August 28 to September 1, 2017	Pending: Preliminary VAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data are unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Investigator

1. Lisa Gore, M.D./Study CA180226

The inspection was conducted from July 24 to 28, 2017. A total of (b) (4) subjects were screened, and (b) (4) subjects were enrolled. One study patient discontinued due to disease progression and another study subject discontinued due to compliance problems. The study is ongoing. A complete audit of the subjects' records enrolled at this site was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. No Form FDA 483 (Inspectional Observations) was issued.

2. Rocio Cardos, M.D./Study CA180226

The inspection was conducted from August 28 to September 1, 2017. A total of (b) (4) subjects were screened, (b) (4) subjects were enrolled. One patient discontinued due to lack of treatment response. The study is ongoing for the remaining seven subjects who received treatment. An audit of all the subjects' records enrolled at this site was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

A Form FDA 483 was issued for lack of written assurance of continuing Ethics Committee approval between September and December in 2012 (approval previously valid through September 2012), and from December 2014 to March 2016 (approval previously valid through December 2014).

OSI Reviewer's Comment: Although a regulatory violation, the above inspectional observation was not considered significant because:

a. *The initial lapse in continuing approval, the request for renewal of approval was sent late by the CI and was misfiled at the Ethics Committee office.*
b. *The principal investigator did appropriately report SAEs and Suspected Unexpected Serious Adverse Reactions (SUSARs) to the Ethics Committee (EC), according to EC requirements. Despite not having formal continuous approval, communications were still being sent between the clinical investigator and the Ethics Committee.*
c. *The site clinical investigator provided his signature to updates of the study protocol and amendments accordingly.*

There was no evidence that patient harms resulted from delays in the approval of the most recent Ethics Committee protocol approvals.

{See appended electronic signature page}

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/s/

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