09-J1000-43

Original Effective Date: 01/01/12

Reviewed: 01/09/19

Revised: 02/15/19

Subject: Dasatinib (Sprycel®) Tablets

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Dasatinib (Sprycel), a second-generation tyrosine kinase inhibitor (TKI), was approved by the US Food and Drug Administration (FDA) in June 2006 for the treatment of all phases of chronic myeloid leukemia (CML) resistant to or intolerant of prior therapy and for Philadelphia chromosome-positive (Ph+) acute lymphocytic leukemia (ALL) resistant or intolerant of prior therapy. The approval was expanded in October 2010 to include treatment of newly diagnosed Ph+ CML in chronic phase. The FDA had previously granted dasatinib orphan designation status for the treatment of CML and the treatment of Ph+ ALL in November 2005. In November 2017, the FDA approved dasatinib for the treatment of pediatric patients one year of age and older with Ph+ CML in chronic phase. In December 2018, the FDA approved dasatinib for the treatment of pediatric patients one year of age and older with newly diagnosed Ph+ ALL in combination with chemotherapy.

Chronic myeloid leukemia (CML) is a hematopoietic stem cell disease characterized by a reciprocal translocation between chromosomes 9 and 22, resulting in the formation of the Philadelphia (Ph) chromosome. CML occurs in three different phases (chronic, accelerated, and blast phase) and is usually diagnosed in the chronic phase. Untreated chronic phase CML will eventually progress to advanced phase disease in 3 to 5 years. The National Comprehensive Cancer Network (NCCN) CML guidelines provide treatment recommendations for all three phases. The NCCN guidelines for CML (Version 1.2019) list imatinib, bosutinib, nilotinib, and dasatinib as category 1 options for the initial first-line treatment of chronic-phase CML in patients with a low-risk Sokal or Hasford score. For CP-CML patients with an intermediate- or high-risk score, imatinib is listed as category 2A option, while bosutinib, nilotinib, and dasatinib (second-generation TKIs) are listed as category 1 options. In addition, bosutinib, dasatinib and nilotinib have a footnote stating “Based on long-term follow-up data from the DASISION and ENESTnd trials and preliminary data from the BFORE trial, second generation TKIs (dasatinib, nilotinib, or bosutinib)

are preferred for patients with an intermediate- or high-risk Sokal or Hasford score, especially for young women whose goal is to achieve a deep and rapid molecular response and eventual drug discontinuation of TKI therapy for fertility purposes." The imatinib listing for intermediate- or high-risk scores includes a footnote stating, "Imatinib may be preferred for older patients with comorbidities such as cardiovascular disease." Age, toxicity profile of the TKI, tolerance of adverse effects, and comorbid conditions also may affect initial choice of treatment. Allogenic hematopoietic cell transplantation (HCT) is no longer recommended as first-line treatment option for patient with CP-CML. If the 3-month response milestone (i.e., early molecular response) is not achieved after first-line TKI therapy, patients are considered to be a high risk for disease progression and alternative treatment options should be considered. Evaluation for allogenic HCT is recommended if the response milestones are not achieved at 3, 6, and 12 months. For patients who do not achieve response milestone or those with a loss of response, BCR-ABL1 mutational analysis is recommended, as it is helpful in the selection of subsequent TKI therapy. In vitro studies have shown that some mutations confer resistance specifically to one second generation TKI and not the other. For example, T315A, V299L, and F359V confer resistance to dasatinib only, whereas Y253H, E255K/V, L273M, and F359V specifically to nilotinib.

Acute lymphoblastic leukemia (ALL) is a heterogeneous hematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood and other organs. The long-term prognosis for adults with ALL remains poor, with cure rates of only 30% to 40%. The treatment approach to ALL represents one of the most complex and intensive programs in cancer therapy. In general, treatment phases can be largely grouped into induction, consolidation, and maintenance. The advent of novel agents targeted to specific genetic abnormalities, such as those associated with Ph+ ALL, or to specific cell antigens, has contributed to improvements in outcomes in some subtypes of ALL. These agents include BCR-ABL selective TKIs for Ph+ ALL. The NCCN guidelines for ALL (Version 1.2018) list dasatinib as a category 2A treatment option in various induction protocol for AYA (adolescent and young adult) and adult patients, as a TKI option in post-induction maintenance regimens, and for relapsed or refractory ALL in patients with Y253H, E255K/V, or F359V/C/I BCR-ABL1 mutations.

The NCCN Guidelines for Bone Cancer (Version 1.2019) list dasatinib monotherapy as a Category 2A recommendation for the treatment of chondrosarcoma with widespread metastatic disease and for the treatment of recurrent chordoma.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of dasatinib (Sprycel) meets the definition of **medical necessity** when **ALL** of the following criteria are met ("1", "2", "3"):

1. Member is **NOT** taking another tyrosine kinase inhibitor (TKI) (i.e., imatinib, nilotinib, bosutinib, or ponatinib) or omacetaxine mepesuccinate (Synribo) concurrently with dasatinib.
2. Dosage of dasatinib does not exceed 180 mg daily, and will be achieved using the fewest number of tablets per day.
3. The member is receiving treatment for **ANY** of the following conditions ("a" to "f"), and **ALL** associated criteria are met:

a. Chronic-, accelerated-, or blast-phase Philadelphia (Ph) chromosome-positive or BCR-ABL1-positive chronic myeloid leukemia (CML) (including post-transplant relapse), **AND** the member does **NOT** have a F317L/V/I/C, T315A, V299L, or T315I mutation (only applicable if a BCR-ABL kinase domain mutation analysis has been performed).

b. Ph-positive or BCR-ABL1-positive acute lymphoblastic leukemia (ALL) (induction, consolidation, and/or maintenance therapy), **AND** the member does **NOT** have a F317L/V/I/C, T315A, V299L, or T315I mutation (only applicable if a BCR-ABL kinase domain mutation analysis has been performed).

c. Progressive gastrointestinal stromal tumors (GIST), and **BOTH** of the following ("i" and "ii"):

   i. Member has a documented platelet derived growth factor receptor alpha (PDGFRA) D842V mutation (confirmatory laboratory documentation of mutation must be submitted).

   ii. Member has had an inadequate response, persistent intolerable adverse effects, or contraindications to at least **TWO** first-line GIST treatments [i.e., imatinib, sunitinib (Sutent), or regorafenib (Stivarga)] (the specific adverse effects or contraindications must be provided).

d. Chordoma (a type of bone cancer), and **BOTH** of the following ("i" and "ii"):

   i. Dasatinib is being used as single-agent therapy

   ii. Member has recurrent disease

e. Chondrosarcoma (a type of bone cancer), and **BOTH** of the following ("i" and "ii"):

   i. Dasatinib is being used as single-agent therapy

   ii. Member has widespread metastatic disease

f. An FDA-approved or NCCN-supported diagnosis (not previously listed above), and **EITHER** of the following is met ("i" or "ii"):

   i. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) AND member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)

   ii. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation

Approval duration: 6 months

Continuation of dasatinib (Sprycel) meets the definition of medical necessity when **ALL** of the following criteria are met ("1", "2", "3", "4" and "5"):

1. The member has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of CML, ALL, GIST, chondrosarcoma, chordoma, or other FDA-approved or NCCN-supported diagnosis, **OR** the member has previously met all indication-specific criteria.
2. Member does **NOT** have a F317L/V/I/C, T315A, V299L, or T315I mutation (only applicable if a BCR-ABL kinase domain mutation analysis has been performed and does **NOT** apply if dasatinib is being used for treatment of GIST).
3. Member's disease has not progressed during treatment with dasatinib (unless treatment is for GIST).
4. Member is **NOT** taking another TKI (i.e., imatinib, nilotinib, bosutinib, or ponatinib) or omacetaxine concurrently with dasatinib.

5. Dosage of dasatinib does not exceed 180 mg daily and will be achieved using the fewest number of tablets per day.

Approval duration: 1 year

NOTE: Quest Diagnostics® can perform the BCR-ABL kinase domain mutation test and the c-KIT mutations with reflex to PDGFRA mutations for GIST test (to detect D842V mutation). Current guidelines recommend checking mutational analysis in the following situations: if there is inadequate initial response, any sign of loss of response, and in disease progression to accelerate-phase or blast-phase CML (CML-AP and CML-BP, respectively).

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved: dasatinib is indicated for the treatment of adults with newly diagnosed 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 with imatinib; and adults with Ph+ acute lymphoblastic leukemia (ALL) with resistance or intolerance to prior therapy. Dasatinib is also indicated for the treatment of pediatric patients (one year of age or older) with Ph+ CML in chronic phase or with newly diagnosed Ph+ ALL in combination with chemotherapy. Dasatinib is administered orally and can be taken with or without food. The tablets should not be crushed or chewed. The recommended dose for treatment of adults with chronic phase CML is 100 mg once daily. The recommended dose for the other FDA-approved indications for adults is 140 mg once daily. In clinical studies, treatment was continued until disease progression or until no longer tolerated by the patient. The dosage for pediatric patient is weight-based and can be found in the package labeling for both CML and ALL. Dosage modifications for pediatric patients can also be found in the labeling.

Dose Modifications for Adults

- **Dose Escalation:** Dose escalation to 140 mg once daily in persons with chronic phase CML or 180 mg daily in persons with advanced phase CML and Ph+ ALL is an option in persons who do not achieve a hematologic or cytogenetic response at the recommended starting doses.
- **Concomitant Strong CYP3A4 Inducers:** Use of concomitant strong CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital, St. John's Wort) may decrease dasatinib plasma concentrations and should be avoided. If co-administration cannot be avoided, a dasatinib dose increase should be considered with subsequent careful monitoring for toxicity.
- **Concomitant Strong CYP3A4 Inhibitors:** Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase dasatinib plasma concentrations and should be avoided. Avoid grapefruit products since they may also increase serum concentrations of dasatinib. If co-administration cannot be avoided, consider a decrease in the dasatinib dose. Based on pharmacokinetic studies, a dose decrease to 20 mg daily should be considered for patients taking 100 mg daily. For patients taking 140 mg daily, a dose decrease to 40 mg daily should be considered. There are no clinical data with these dose adjustments. If not tolerated after a dose reduction, either the strong CYP3A4 inhibitor must be discontinued, or dasatinib should be stopped until treatment with the inhibitor has ceased. When the strong inhibitor is discontinued, a washout period of approximately 1 week should be allowed before the dasatinib dose is increased.

- **Hepatic Impairment:** No dosage adjustment is necessary in patients with hepatic impairment; however, caution is recommended.
- **Myelosuppression**: Myelosuppression can be managed by dose interruption, dose reduction, or discontinuation of therapy. Hematopoietic growth factor has been used in persons with resistant myelosuppression. The Table describes guidelines for dose modifications.

Table: Dose Adjustments for Neutropenia and Thrombocytopenia in Adults		
Chronic Phase CML (starting dose 100 mg once daily)	ANC <0.5 × 10^9/L or Platelets <50 × 10^9/L	1. Stop dasatinib until ANC ≥1 × 10^9/L and platelets ≥50 × 10^9/L 2. Resume treatment with dasatinib at the original starting dose if recovery occurs in ≤7 days. 3. If platelets <25 × 10^9/L or recurrence of ANC <0.5 × 10^9/L for >7 days, repeat Step 1 and resume dasatinib 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 (for patients resistant or intolerant to prior therapy including imatinib).
Accelerated and Blast Phase CML and Ph+ ALL (starting dose 140 mg once daily)	ANC <0.5 × 10^9/L or Platelets <10 × 10^9/L	1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukemia, stop dasatinib until ANC ≥1 × 10^9/L and platelets ≥20 × 10^9/L and resume at the original starting dose 3. If recurrence of cytopenia, repeat Step 1 and resume dasatinib 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		

Drug Availability: dasatinib is available as a 20-, 50-, 70-, 80-, 100-, and 140 mg tablet.

PRECAUTIONS:

CONTRAINDICATIONS

- None

WARNINGS

- **Myelosuppression:** Treatment with dasatinib is associated with severe thrombocytopenia, neutropenia, and anemia and may require dose interruption or reduction. 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. In pediatric patients with Ph+ ALL, perform CBCs prior to the start of each block of chemotherapy and as clinically indicated. During the consolidation blocks of chemotherapy, perform CBCs every 2 days until recovery.
- **Bleeding Events:** In addition to causing thrombocytopenia, dasatinib can cause platelet dysfunction. CNS and gastrointestinal hemorrhages, including fatalities have occurred, and are usually associated with severe thrombocytopenia. Severe hemorrhage may require treatment interruptions and transfusions. Use with caution in persons requiring medications that inhibit platelet function or anticoagulants.

- **Fluid retention:** Dasatinib is associated with fluid retention, sometimes severe, including ascites, edema, pleural effusions, and pericardial effusions. Manage with appropriate supportive care measures (e.g., diuretics, short-term steroids). Fluid retention events are less frequently with once daily dosing than with other dosing regimens.
- **QT prolongation:** Use with caution in persons who have or may develop QT prolongation (e.g., hypokalemia or hypomagnesemia, congenital long QT syndrome, or concomitant medications know to prolong the QT interval). Correct hypokalemia or hypomagnesemia prior to administration.
- **Cardiovascular events:** Dasatinib can cause cardiac dysfunction. Monitor members for signs or symptoms consistent with cardiac dysfunction and treat appropriately.
- **Pulmonary Arterial Hypertension:** Dasatinib may increase the risk of developing pulmonary arterial hypertension (PAH) which may occur any time after initiation, including after more than 1 year of treatment and may be reversible on discontinuation. Evaluate members for signs and symptoms of underlying cardiopulmonary disease prior to initiating dasatinib and during treatment. If PAH is confirmed, permanently discontinue dasatinib.
- **Severe dermatologic reactions**: Individual cases of severe mucocutaneous dermatologic reactions, including Stevens-Johnson syndrome and erythema multiforme, have been reported.
- **Tumor Lysis Syndrome**: Tumor lysis syndrome has been reported. Maintain adequate hydration and correct uric acid levels prior to initiating therapy with dasatinib.
- **Embryo-fetal toxicity:** Dasatinib can cause fetal harm when administered to a pregnant woman. Women should be advised of the potential hazard to the fetus and avoid becoming pregnant.
- **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.

BILLING/CODING INFORMATION:

HCPCS Coding

J8999	Prescription drug, oral, chemotherapeutic, NOS

ICD-10 Diagnosis Codes That Support Medical Necessity

C40.00 – C40.92	Malignant neoplasm of bone and articular cartilage of limbs
C41.0 – C41.9	Malignant neoplasm of bone and articular cartilage of other and unspecified sites
C49.A0 - C49.A9	Gastrointestinal stromal tumor
C49.4	Malignant neoplasm of connective and soft tissue of abdomen
C49.8	Malignant neoplasm of overlapping sites of connective and soft tissue
C49.9	Malignant neoplasm of connective and soft tissue, unspecified
C72.0	Malignant neoplasm of spinal cord
C72.1	Malignant neoplasm of cauda equina
C91.00	Acute lymphoblastic leukemia not having achieved remission
C91.01	Acute lymphoblastic leukemia, in remission
C91.02	Acute lymphoblastic leukemia, in relapse
C92.10	Chronic myeloid leukemia, BCR/ABL-positive, not having achieved remission
C92.11	Chronic myeloid leukemia, BCR/ABL-positive, in remission
C92.12	Chronic myeloid leukemia, BCR/ABL-positive, in relapse

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT.**

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

DEFINITIONS:

Accelerated Phase CML: is a phase of chronic myelogenous leukemia in which the disease is progressing.

Acute lymphoblastic leukemia: an aggressive (fast-growing) type of leukemia (blood cancer) in which too many immature white blood cells are found in the blood and bone marrow. Also called acute lymphocytic leukemia and ALL.

Blast Phase CML: is the final phase in the evolution of CML, and behaves like an acute leukemia, with rapid progression and short survival.

Chronic Phase CML: approximately 85% of members with CML are in the chronic phase at the time of diagnosis. During this phase, members are usually asymptomatic or have only mild symptoms of fatigue, left side pain, joint and/or hip pain, or abdominal fullness.

Chronic Myelogenous Leukemia (CML): also known as chronic granulocytic leukemia (CGL), is a cancer of the white blood cells. It is a form of leukemia characterized by the increased and unregulated growth of predominantly myeloid cells in the bone marrow and the accumulation of these cells in the blood.

Cytogenetic: is a branch of genetics that is concerned with the study of the structure and function of the cell, especially the chromosomes. It includes routine analysis of G-banded chromosomes, other cytogenetic banding techniques, as well as molecular cytogenetics such as fluorescent in situ hybridization (FISH) and comparative genomic hybridization (CGH).

Induction Chemotherapy: the use of drug therapy as the initial treatment for patients presenting with advanced cancer that cannot be treated by other means.

Philadelphia chromosome or Philadelphia translocation: is a specific chromosomal abnormality that is associated with chronic myelogenous leukemia (CML).

RELATED GUIDELINES:

Allogeneic Bone Marrow and Stem Cell Transplantation, 02-38240-01

Bosutinib (Bosulif) Tablets, 09-J1000-84

Cytogenetic Studies (Chromosomal Studies), 05-82000-18

Imatinib (Gleevec) Tablets, 09-J1000-46

Nilotinib (Tasigna) Capsules, 09-J1000-48

Sunitinib Malate (Sutent) Capsules, 09-J1000-51

Regorafenib (Stivarga), 09-J1000-83

Ponatinib (Iclusig) Tablet, 09-J1000-89

Omacetaxine (Synribo) Injection, 09-J1000-87

OTHER:

None

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 01/09/19.

GUIDELINE UPDATE INFORMATION:

01/01/12	New Medical Coverage Guideline.
11/15/12	Review and revision to guideline; consisting of reformatting position statement, added contraindications, added warnings, updated coding, program exceptions, related guidelines and references.
03/15/13	Review and revision to guideline; consisting of revising and reformatting position statement, revising and reformatting description, dosage/administration, and precautions section; adding pertinent definitions and related guidelines; updating references and coding.
03/15/14	Review and revision to guideline; consisting of reformatting and revising position statement; updating references, coding, and program exceptions.
03/15/15	Review and revision to guideline; consisting of revising position statement and updating the description, dosage/administration, warnings, and references.
11/01/15	Revision: ICD-9 Codes deleted.
03/15/16	Review and revision to guideline consisting of description, position statement, definitions, and references.
09/15/16	Revision to guideline consisting of updating the position statement and definitions.
10/01/16	Revision: ICD-10 code updates.
01/15/17	Revision to guideline consisting of updating the description section, position statement, and references based on updated NCCN guidelines.
03/15/17	Review and revision to guideline consisting of updating the position statement, description section, dosage/administration section, precautions section, and references.
12/15/17	Revision to guideline consisting of updating the position statement to remove imatinib as prerequisite therapy for low-risk CML and Ph+ ALL.
02/15/18	Review and revision to guideline consisting of updates to description, position statement, dosage/administration, billing/coding, definitions, other, and references sections.
02/15/19	Review and revision to guideline consisting of updates to description, position statement, dosage/administration, precautions, billing/coding, definitions, and references sections.