09-J1000-48

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Reviewed: 01/09/19

Revised: 02/15/19

Subject: Nilotinib (Tasigna®) Capsules

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:

Nilotinib (Tasigna), a second-generation tyrosine kinase inhibitor (TKI), was approved by the US Food and Drug Administration (FDA) in October 2007 for the treatment of adults with chronic-phase (CP) and accelerated-phase (AP) Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) resistant to or intolerant of prior treatment with imatinib (Gleevec). In December 2017, nilotinib became the first TKI to include information in the labeling regarding the eligibility of certain patients to discontinue treatment after 3 years. In March 2018, the indication was expanded to include the treatment of pediatric patients (1 year of age or older) with either newly diagnosed Ph+ CML in chronic phase, or chronic phase Ph+ CML with resistance or intolerance to prior TKI therapy. Nilotinib has also shown efficacy in the treatment of Ph+ acute lymphoblastic leukemia (ALL) and gastrointestinal stromal tumors (GISTs). The FDA had previously granted nilotinib orphan designation status for the treatment of CML in 2006.

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 heterogenous hematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood and other organs. ALL represents approximately 20% of all leukemias among adults. 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. All phases of treatment also include central nervous system (CNS) prophylaxis and/or treatment to clear leukemic cells within sites that cannot be readily accessed with systemic chemotherapy due to the blood-brain barrier. During the past decade, 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 nilotinib as a category 2A treatment option in various induction protocols 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 F317L/V/I/C, T315A, or V299L BCR-ABL1 mutations.

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 nilotinib (Tasigna) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1", "2", and "3"):

1. Member is **NOT** taking another tyrosine kinase inhibitor (TKI) (i.e., imatinib, dasatinib, bosutinib, or ponatinib) or omacetaxine mepesuccinate (Synribo) concurrently with nilotinib.
2. Dosage of nilotinib does not exceed 400 mg twice daily (i.e., 800 mg total per day) and will be achieved using the fewest number of capsules per day.
3. The member is receiving treatment for **ANY** of the following conditions ("a", "b", "c", or "d"), 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)

   i. Member does **NOT** have a Y253H, E255K/V, F359V/C/I, or T315I mutation (only applicable if a BCR-ABL kinase domain mutation analysis has been performed)

   ii. **EITHER** of the following ("a" or "b"):

      a. Member has an intermediate- or high-risk Sokal or Hasford score as determined prior to treatment initiation (at least one calculated score must be provided)

      b. Member has previously tried imatinib treatment and **EITHER** had an inadequate initial treatment response or relapse during treatment **OR** had persistent intolerable adverse effects despite appropriate dose modification (the specific adverse effect must be provided), **UNLESS** either of the following apply:

         - Member has documented genetic resistance to imatinib (lab documentation of F317L/V/I/C, T315A, or V299L mutation must be submitted)
         - Member has an FDA-labeled contraindication to imatinib (the specific contraindication must be provided)

b. Ph-positive or BCR-ABL1-positive acute lymphoblastic leukemia (ALL) (induction, consolidation, and/or maintenance therapy), **AND** the member does **NOT** have an Y253H, E255K/V, F359V/C/I, or T315I mutation (only applicable if a BCR-ABL kinase domain mutation analysis has been performed).

c. Progressive gastrointestinal stromal tumors (GIST),

   i. Member meets any of the following in reference to at least **TWO** first-line GIST treatments [i.e., imatinib, sunitinib (Sutent), or regorafenib (Stivarga)] one of which must be imatinib:

      - Did not achieve recommended initial treatment goals or experienced disease relapse during treatment
      - Had persistent intolerable adverse effects despite appropriate dose modification (the specific adverse effect must be provided)
      - Has documented genetic resistance (lab documentation must be submitted)
      - Has an FDA-labeled contraindication (the specific contraindication must be provided)

d. 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 nilotinib (Tasigna) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

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, or other FDA-approved or NCCN-supported diagnosis, **OR** the member has previously met all indication-specific criteria

2. Member does **NOT** have a Y253H, E255K/V, F359V/C/I, or T315I mutation (only applicable if a BCR-ABL kinase domain mutation analysis has been performed and does **NOT** apply if nilotinib is being used for treatment of GIST).
3. Member's disease has not progressed during treatment with nilotinib (unless treatment is for GIST).
4. Member is **NOT** taking another TKI (i.e., imatinib, dasatinib, bosutinib, or ponatinib) or omacetaxine concurrently with nilotinib.
5. Dosage of nilotinib does not exceed 400 mg twice daily (800 mg total per day) and will be achieved using the fewest number of capsules per day.

Approval duration: 1 year

NOTE: Quest Diagnostics® can perform the BCR-ABL kinase domain mutation test. Current NCCN 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: nilotinib is indicated for the following: (1) the treatment of adult and pediatric patients greater than or equal to 1 year of age with newly-diagnosed Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in chronic phase (CP), (2) the treatment of CP and accelerated phase (AP) Ph+ CML in adults resistant to or intolerant of prior therapy that included imatinib, and (3) the treatment of pediatric patients greater than or equal to 1 year of age with CP Ph+ CML with resistance or intolerance to prior TKI therapy. The recommended adult dose is 300 mg orally twice daily for newly diagnosed Ph+ CML-CP and 400 mg twice daily for resistant or intolerant Ph+ CML-CP and CML-AP. The recommended dose for pediatric patients is 230 mg/m^2 twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg) [see Table 1 in the product labeling for dosage recommendations for different body surface area (BSA) ranges]. If needed, attain the desired dose by combining different strengths of capsules. Nilotinib should be administered approximately 12 hours apart and must be taken on an empty stomach. The capsules should be swallowed whole with water. Discontinuation of treatment can be considered for certain patient who have received treatment for at least 3 years. See the package labeling for the recommended criteria and monitoring requirements. Patients, who stop therapy and lose response, should be re-initiated on treatment within 4 weeks at the previous dose level.

Dose Modifications for Adults (refer to the product labeling for the pediatric dosage recommendations)

- **Concomitant Strong CYP3A4 Inhibitors:** Avoid the concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole). Avoid grapefruit products since they may also increase serum concentrations of nilotinib. Should treatment with any of these agents be required, therapy with nilotinib should be interrupted. If patients must be coadministered a strong CYP3A4 inhibitor consider a dose reduction to 300 mg once daily in patients with resistant or intolerant Ph+ CML or to 200 mg once daily in patients with newly diagnosed Ph+ CML-CP. There are no clinical data with this dose adjustment in patients receiving strong CYP3A4

inhibitors. Also, monitor closely for prolongation of the QT interval. If a strong inhibitor is discontinued, a washout period should be allowed before the nilotinib dose is adjusted upward to the indicated dose.

- **Concomitant Strong CYP3A4 Inducers**: Avoid the concomitant use of strong CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, St. John's Wort). Based on the nonlinear pharmacokinetic profile of nilotinib, increasing the dose of nilotinib when coadministered with such agents is unlikely to compensate for the loss of exposure.
- **Selected Non-hematologic Laboratory Abnormalities**

Table 1

Dose Adjustments for Selected Non-hematologic Laboratory Abnormalities	
Elevated serum lipase or amylase ≥ Grade 3	1. Withhold nilotinib, and monitor serum lipase or amylase 2. Resume treatment at 400 mg once daily if serum lipase or amylase returns to ≤ Grade 1
Elevated bilirubin ≥ Grade 3	1. Withhold nilotinib, and monitor bilirubin 2. Resume treatment at 400 mg once daily if bilirubin returns to ≤ Grade 1
Elevated hepatic transaminases ≥ Grade 3	1. Withhold nilotinib, and monitor hepatic transaminases 2. Resume treatment at 400 mg once daily if hepatic transaminases returns to ≤ Grade 1

- **Myelosuppression - Absolute Neutrophil Count (ANC) <1 x 10^9/L and/or Platelet Counts <50 x 10^9/L**
    1. Stop nilotinib, and monitor blood counts
    2. Resume within 2 weeks at prior dose if ANC >1 x 10^9/L and platelets >50 x 10^9/L
    3. If blood counts remain low for >2 weeks, reduce the dose to 400 mg once daily
- **QT Interval Prolongation: ECGs With QTc > 480 msec**
    1. Withhold nilotinib, and perform an analysis of serum potassium and magnesium, and if below lower limit of normal, correct to within normal limits. Concomitant medication usage must be reviewed.
    2. Resume within 2 weeks at prior dose if QTcF returns to < 450 msec and to within 20 msec of baseline.
    3. If QTcF is between 450 msec and 480 msec after 2 weeks, reduce the dose to 400 mg once daily.
    4. If, following dose-reduction to 400 mg once daily, QTcF returns to > 480 msec, nilotinib should be discontinued.
    5. An ECG should be repeated approximately 7 days after any dose adjustment.

Table 2

Dose Adjustments for Hepatic Impairment (At Baseline)		
Indication	**Child-Pugh Class**	**Dose**

Newly diagnosed Ph+ CML	Any (A, B, or C)	Initial dose: 200 mg twice daily; escalate dose to 300 mg twice daily based on tolerability
Resistant or intolerant Ph+ CML	A, B	Initial dose 300 mg twice daily; escalate dose to 400 mg twice daily based on tolerability
	C	Initial dose 200 mg twice daily; sequential escalation to 300 mg twice daily and then to 400 mg twice daily based on tolerability

Drug Availability: nilotinib is available as 50 mg (red and light yellow), 150 mg (red) and 200 mg (light yellow) capsules.

PRECAUTIONS:

CONTRAINDICATIONS

- Do not use in patients with hypokalemia, hypomagnesemia, or long QT syndrome.

BOXED WARNING:

- Nilotinib prolongs the QT interval. Prior to administration and periodically, monitor for hypokalemia or hypomagnesemia and correct deficiencies. Obtain ECGs to monitor the QTc at baseline, seven days after initiation, and periodically thereafter, and follow any dose adjustments.
- Sudden deaths have been reported in members receiving nilotinib. Do not administer to members with hypokalemia, hypomagnesemia, or long QT syndrome.
- Avoid use of concomitant drugs known to prolong the QT interval and strong CYP3A4 inhibitors.
- Members should avoid food two hours before and one hour after taking dose.

WARNINGS

- **Myelosuppression:** Treatment with nilotinib can cause severe thrombocytopenia, neutropenia, and anemia. Perform complete blood cell counts (CBCs) every 2 weeks for the first 2 months and then monthly thereafter, or as clinically indicated. Reversible by withholding dose; dose reduction may be required.
- **QT prolongation:** Nilotinib prolongs the QT interval. Correct hypokalemia or hypomagnesemia prior to administration and monitor periodically. Avoid concomitant administration of drugs known to prolong the QT interval and strong CYP3A4 inhibitors. Use with caution in patients with hepatic impairment. Obtain ECGs at baseline, seven days after initiation, and periodically thereafter. The same monitoring should be done following any dose adjustments.
- **Sudden deaths:** Sudden deaths have been reported in members with resistant or intolerant CML treated with nilotinib in clinical studies (0.3%). The relative early occurrence of some of the deaths relative to the initiation of nilotinib suggests the possibility that ventricular repolarization abnormalities may have contributed to their occurrence.
- **Cardiac and Arterial Vascular Occlusive Events:** Events including ischemic heart disease, peripheral arterial occlusive disease and ischemic cerebrovascular events have been reported in patients with newly diagnosed Ph+ CML receiving nilotinib. Cardiovascular status should be evaluated and cardiovascular risk factors monitored and managed during therapy.
- **Pancreatitis and elevated serum lipase:** Check serum lipase monthly or as clinically indicated. If lipase elevations are accompanied by abdominal symptoms, interrupt doses and consider appropriate diagnostics to exclude pancreatitis. Administer with caution to persons with a history of pancreatitis.

- **Hepatotoxicity:** The use of nilotinib may result in elevations in alkaline phosphatase, AST/ALT, and bilirubin. Check hepatic function tests monthly or as clinically indicated.
- **Tumor lysis syndrome:** Cases have been reported in nilotinib treated patients with resistant or intolerant CML. Due to potential for tumor lysis syndrome, maintain adequate hydration and correct uric acid levels prior to initiating therapy.
- **Electrolyte abnormalities:** The use of nilotinib can cause hyperkalemia, hypocalcemia, hypokalemia, hyponatremia, and hypophosphatemia. Electrolyte abnormalities must be corrected prior to initiating nilotinib. Monitor these electrolytes periodically during therapy.
- **Drug interactions:** Avoid concomitant use of strong inhibitors or inducers of CYP3A4. If patients must be coadministered a strong CYP3A4 inhibitor, dose reduction should be considered and the QT interval should be monitored closely.
- **Total gastrectomy:** The exposure of nilotinib is reduced in members with total gastrectomy. Consider more frequent follow-up of these patients. Consider dose increase or alternative therapy in patients with total gastrectomy.
- **Food effects**: Food increases blood levels of nilotinib. Avoid food 2 hours before and 1 hour after a dose.
- **Lactose intolerance:** Because the capsules contain lactose, nilotinib is not recommended for persons with rare hereditary problems of galactose intolerance, severe lactase deficiency with a severe degree of intolerance to lactose-containing products, or glucose-galactose malabsorption.
- **Hepatic function impairment:** Nilotinib exposure is increased in patients with impaired hepatic function. Use a lower starting dose for patients with mild to severe hepatic impairment (at baseline) and monitor the QT interval frequently.
- **Hemorrhage**: Hemorrhage from various sites was reported in patients with newly diagnosed CML and observed in the postmarketing reports of patients receiving nilotinib therapy.
- **Fluid retention**: Pericardial effusion, pleural effusion, and severe fluid retention have occurred in patients receiving nilotinib. Monitor patients for signs and symptoms such as unexpected rapid weight gain, swelling, and shortness of breath.
- **Embryo-fetal toxicity**: Fetal harm can occur when administered to a pregnant woman. Women should be advised not to become pregnant when taking nilotinib.

BILLING/CODING INFORMATION:

HCPCS Coding

J8999	Prescription drug, oral, chemotherapeutic, nos

ICD-10 Diagnosis Codes That Support Medical Necessity

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
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).

Relapse: the return of a disease or the signs and symptoms of a disease after a period of improvement. Specifically for CML a relapse is defined as “any sign of loss response” (defined as hematologic or cytogenic relapse). A 1-log increase in BCR-ABL transcript levels with loss of MMR should prompt bone marrow evaluation for loss of complete cytogenic response is not itself defined as relapse.

Refractory: cancer that does not respond to treatment; the cancer may be resistant at the beginning of treatment or it may become resistant during treatment. Also called resistant cancer.

RELATED GUIDELINES:

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

Bosutinib (Bosulif) Tablets, 09-J1000-84

Dasatinib (Sprycel) Tablets, 09-J1000-43

Imatinib (Gleevec) Tablets, 09-J1000-46

Sunitinib (Sutent), 09-J1000-51

Regorafenib (Stivarga), 09-J1000-83

Ponatinib (Iclusig) Tablet, 09-J1000-89

Omacetaxine (Synribo) Injection, 09-J1000-87

OTHER:

CML Risk Scores

Study	Calculation	Risk Definition by Calculation
Sokal et al, 1984	Exp 0.0116 x (age in years – 43.4) + (spleen – 7.51) + 0.188 x [(platelet count/700)^2 – 0.562] + 0.0887 x (blast cell -2.10)	• Low: <0.8 • Intermediate: 0.8 to 1.2 • High: >1.2
Hasford et al, 1998	0.666 when age ≥50 years + (0.042 x spleen) + 1.0956 when platelet count >1,500 x 10^3/L + (0.0584 x blast cells) + 0.20399 when basophils >3% + (0.0413 X eosinophils) x 100	• Low: ≤780 • Intermediate: 781 to 1,480 • High: >1,480

Age is in years. Spleen is in centimeters below the costal margin (maximum distance). Blast cells, eosinophils, and basophils are in percents of peripheral blood differential. All factors must be collected prior to any treatment.

Online risk calculator can be found at: http://www.icsg.unibo.it/rrcalc.asp

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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 updating position statement, adding contraindications, updating precautions, coding, program exceptions, related guidelines and references.
03/15/13	Review and revision to guideline; consisting of reformatting and revising position statement to include treatment of acute lymphoblastic leukemia; reformatting and revising description, dosage/administration, and precautions sections; adding definitions and related guidelines; and updating coding and references.
03/15/14	Review and revision to guideline; consisting of reformatting/revising position statement; reformatting precautions section; updating program exceptions and references.
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.
02/15/18	Review and revision to guideline consisting of updates to description, position statement, dosage/administration, billing/coding, definitions, and references sections.
05/15/18	Revision to guideline consisting of updates to description, dosage/administration, and references sections based on the new FDA-approved indication for pediatric patients.
02/15/19	Review and revision to guideline consisting of updates to description, position statement, dosage/administration, billing/coding, definitions, other, and references sections.