09-J1000-89

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Reviewed: 01/09/19

Revised: 02/15/19

Next Review: 01/08/20

Subject: Ponatinib (Iclusig®) 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:

Ponatinib (Iclusig) is an oral multi-tyrosine kinase inhibitor (TKI) approved by the US Food and Drug Administration (FDA) in December 2012 for the treatment of adults with chronic myelogenous leukemia (CML) (chronic phase, accelerated phase, or blast phase) or Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) for whom no other inhibitor TKI therapy is indicated (i.e., imatinib [Gleevec], dasatinib [Sprycel], nilotinib [Tasigna], and bosutinib [Bosulif]). The approval was based on results from a pivotal phase II, single-arm, open-label clinical trial. The FDA had previously granted orphan drug designation status for ponatinib in November 2009 for treatment of both CML and Ph+ ALL. In October 2013, ponatinib was withdrawn from the market by the manufacturer at the request of the FDA due to the risk of life-threatening blood clots and severe narrowing of blood vessels. In December 2013, after implementing an FDA-required Risk Evaluation and Mitigation Strategy (REMS) program that included a communication plan to healthcare providers regarding the serious risk of vascular occlusion and thromboembolism associated with treatment, the manufacturer once again began marketing ponatinib to appropriate patients. In addition, the FDA-approved indication was expanded to include treatment of adult patients with T315I-positive CML (chronic phase, accelerated phase, or blast phase) or T315I-positive Ph+ ALL.

Chronic myelogenous leukemia is a hematopoietic stem cell disease characterized by a reciprocal translocation between chromosomes 9 and 22, resulting in the formation of the Philadelphia 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) 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. One important mutation, the T315I, is known as the "gatekeeper" mutation, as it displays resistance to all TKIs, with the exception of ponatinib. In patient with a T315I mutation, the NCCN lists the following as category 2A treatment options: ponatinib, omacetaxine, allogenic HCT, or clinical trial. Ponatinib includes a footnote stating, "Ponatinib is a treatment option for patients with a T315I mutation or for patients for whom no other TKI is indicated." For the treatment of accelerated or blast phase CML, the NCCN recommends that the TKI selected be based on prior therapy and/or BCR-ABL mutation profile.

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 (e.g., imatinib, dasatinib, and nilotinib). Although TKIs have improved the prognosis for adults with ALL, resistance has been observed and is attributed, at least partly, to the presence of point mutations (e.g., T315I, V299L, and F317L mutations) with the ABL kinase domain. Second generation TKIs, specifically, dasatinib and nilotinib, have shown greater potency in inhibiting BCR-ABL compared with imatinib and retention of anti-leukemic activity in cells with certain imatinib-resistant ABL mutations. However, both agents are rendered inactive in persons with a T315I mutation. In the pivotal phase II study, ponatinib showed substantial activity in subjects with Ph+ leukemias resistant or intolerant to second-generation TKIs, including in heavily pretreated subjects with the T315I mutation. The NCCN guidelines for ALL (Version 1.2018) list ponatinib as a category 2A treatment option in an 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 a T315I BCR-ABL1 mutation. However, the NCCN acknowledges via a footnote that ponatinib is associated with a high frequency of serious vascular events (e.g., stokes, heart attacks, tissue ischemia), and that the FDA indication limits treatment to adult patients with a T315I mutation or for whom no other TKI therapy is indicated.

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 ponatinib (Iclusig) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1", "2", "3", and "'4"):

1. Member is **NOT** taking another tyrosine kinase inhibitor (TKI) (i.e., imatinib, dasatinib, nilotinib, or bosutinib) or omacetaxine mepesuccinate (Synribo) concurrently with ponatinib.
2. Member is receiving treatment for **ANY** of the following conditions ("a", "b", or "c"):
    a. Philadelphia-chromosome positive or BCR-ABL1-positive acute lymphoblastic leukemia (ALL)
    b. Chronic-, accelerated-, or blast-phase Philadelphia (Ph) chromosome-positive or BCR-ABL1-positive chronic myeloid leukemia (CML) (including post-transplant relapse)
    c. 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
3. **EITHER** of the following ("a" or "b"):
    a. Member has tested positive for the T315I BCR-ABL kinase domain mutation (confirmatory laboratory documentation must be submitted)
    b. Member meets any of the following ("i", "ii", or "iii") in reference to **TWO or more** TKI therapies (i.e., imatinib, dasatinib, nilotinib, or bosutinib):
        i. Inadequate therapeutic response after at least 3 months of continuous treatment
        ii. Persistent intolerable adverse effects despite appropriate dose modification (the specific adverse effect must be provided)
        iii. FDA-labeled contraindication (the specific contraindication must be provided)
4. Dosage of ponatinib does not exceed 45 mg daily, and will be achieved using the fewest number of tablets per day.

Approval duration: 6 months

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

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

2. Member's disease has not progressed during treatment with ponatinib.
3. Member is **NOT** taking another TKI (i.e., imatinib, dasatinib, nilotinib, or bosutinib) or omacetaxine concurrently with ponatinib.
4. Dosage of ponatinib does not exceed 45 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. 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: ponatinib is indicated for: (1) the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myelogenous leukemia (CML) or Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated, and (2) the treatment of adult patients with T315I-positive CML (chronic phase, accelerated phase, or blast phase) or T315-positive Ph+ ALL.. The product labeling includes a "Limitations of use" statement of "Iclusig is not indicated and is not recommended for the treatment of patients with newly diagnosed chronic phase CML."

The optimal dose of ponatinib has not been identified. In clinical trials, the starting dose was 45 mg orally once daily with or without food. However, 68% of the patients required dose reductions to 30 mg or 15 mg once daily during the course of therapy. Consider reducing the dose for CP-CML and AP-CML patients who have achieved a major cytogenetic response.. Consider discontinuing if response has not occurred by 3 months (90 days).Tablets should be swallowed whole. To reduce the risk of tumor lysis syndrome, adequate hydration and correction of elevated uric acid levels should be achieved prior to ponatinib initiation.

Dose Modifications

- **Concomitant Use with Strong CYP3A Inhibitors:** Reduce dose to 30 mg once daily when administering ponatinib with strong CYP3A inhibitors (e.g., boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole).
- **Hepatic Impairment**: The recommended starting dose is 30 mg once daily in patients with hepatic impairment (Child-Pugh A, B, or C)
- **Toxicity:** Dose adjusts for toxicity (i.e., myelosuppression and non-hematologic adverse reactions) are depicted in tables 1-3.

Table 1

Suggested dose adjustments for myelosuppression		
	Occurrence	**Re-initiation dose†**
ANC less than 1,000 cells/mm^3 **OR** Platelet count less than 50,000 cells/mm^3	1st	45 mg
	2nd	30 mg
	3rd	15 mg
†Once ANC is greater than 1,500 cells/mm^3 and platelet count is greater than 75,000 cells/mm^3 ANC, absolute neutrophil count		

Table 2

Recommended dose adjustments for hepatic toxicity		
	Dose at Occurrence	**Action**
Elevation of AST or ALT greater than 3 x ULN (Grade 2 or higher)	45 mg	• Interrupt therapy and monitor hepatic function • Resume at 30 mg after ALT and AST is less than 3 x ULN (Grade 1 or less)
	30 mg	• Interrupt therapy and monitor hepatic function • Resume at 15 mg after ALT and AST is less than 3 x ULN (Grade 1 or less)
	15 mg	• Discontinue
Elevation of AST or ALT 3 x ULN or greater (Grade 2 or higher) **AND** elevation of bilirubin greater than 2 x ULN **AND** alkaline phosphatase less than 2 x ULN	Discontinue therapy	
ULN, upper limit of normal for lab performing test		

Table 3

Table 3: Recommended dose adjustments for pancreatitis and lipase elevations		
	Dose at Occurrence	**Action**
Asymptomatic Grade 1 or Grade 2	**ANY**	• Consider therapy interruption or

elevation of serum lipase		dose reduction
Asymptomatic Grade 3 or 4 elevation (greater than 2 x ULN) or Grade 2 pancreatitis (asymptomatic radiologic pancreatis)	45 mg	• Interrupt therapy • Resume at 30 mg once recovery to Grade 1 or less
	30 mg	• Interrupt therapy • Resume at 15 mg once recovery to Grade 1 or less
	15 mg	• Discontinue therapy
Symptomatic Grade 3 pancreatitis	45 mg	• Interrupt therapy • Resume at 30 mg once complete resolution of symptoms and recovery to Grade 1 or less
	30 mg	• Interrupt therapy • Resume at 15 mg once complete resolution of symptoms and recovery to Grade 1 or less
	15 mg	• Discontinue therapy
Grade 4 pancreatitis	Discontinue therapy	
ULN, upper limit of normal for laboratory performing test		

Drug Availability: ponatinib is available as 15, 30, and 45 mg tablet.

PRECAUTIONS:

CONTRAINDICATIONS

- None

BOXED WARNINGS

WARNING: ARTERIAL OCCLUSION, VENOUS THROMBOEMBOLISM, HEART FAILURE, and HEPATOTOXICITY

- **Arterial Occlusion**: Arterial occlusions have occurred in at least 35% of ponatinib -treated patients. Some patients experienced more than 1 type of event. Events observed included fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. Monitor for evidence of arterial occlusion. Interrupt or stop ponatinib immediately for arterial occlusion. A benefit-risk consideration should guide a decision to restart ponatinib therapy.
- **Venous Thromboembolism**: Venous occlusive events have occurred in 6% of ponatinib -treated patients. Monitor for evidence of venous thromboembolism. Consider dose modification or discontinuation of Iclusig in patients who develop serious venous thromboembolism.

- **Heart Failure:** Heart failure, including fatalities, occurred in 9% of ponatinib-treated patients. Monitor cardiac function. Interrupt or stop ponatinib for new or worsening heart failure.
- **Hepatotoxicity:** Hepatotoxicity, liver failure, and death have occurred in ponatinib-treated patients. Monitor hepatic function. Interrupt Iclusig if hepatotoxicity is suspected.

WARNINGS

- **Hypertension:** Monitor for high blood pressure and treat as clinically indicated.
- **Neuropathy:** Monitor for symptoms of peripheral and cranial neuropathy.
- **Ocular toxicity:** Conduct comprehensive eye exams at baseline and periodically during treatment.
- **Pancreatitis:** Monitor serum lipase monthly; elevations may require dose interruption or discontinuation.
- **Hemorrhage:** Interrupt dosing for serious or severe hemorrhage.
- **Fluid retention:** Monitor for signs and symptoms of fluid retention. May require interruption, reduction, or discontinuation of therapy.
- **Cardiac arrhythmias:** Monitor for symptoms of arrhythmia.
- **Myelosuppression:** Thrombocytopenia, neutropenia, and anemia may require dose interruption or reduction. Monitor complete blood counts (CBC) every 2 weeks for 3 months and then monthly and as clinically indicated. Refer to dosage and administration section for recommended dose adjustments.
- **Tumor Lysis Syndrome:** Ensure adequate hydration and correct elevated uric acid levels prior to therapy initiation.
- **Reversible posterior leukoencephalopathy syndrome (RPLS):** Interrupt and resume treatment only once the event is resolved and if the benefit of continued treatment outweighs the risk of RPLS.
- **Compromised wound healing and gastrointestinal perforation:** Temporarily interrupt therapy in members undergoing major surgical procedures.
- **Embryo-Fetal Toxicity:** Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J8999	Prescription drug, oral, chemotherapeutic, NOS

ICD-10 Diagnosis Codes That Support Medical Necessity

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

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

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

Dasatinib (Sprycel) Tablets, 09-J1000-43

Imatinib Mesylate (Gleevec) Tablets, 09-J1000-46

Nilotinib (Tasigna) Capsules, 09-J1000-48

Omacetaxine (Synribo) Injection, 09-J1000-87

OTHER:

None applicable.

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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:

03/15/13	New Medical Coverage Guideline.
12/15/13	No Longer Review
3/15/14	Review and revision to guideline; consisting of revising position statement, updating dosage/administration, precautions, and references.
02/15/15	Review and revision to guideline; consisting of revising position statement, and updating the description, dosage/administration, boxed warning, and references.
11/01/15	Revision: ICD-9 Codes deleted.
03/15/16	Review and revision to guideline consisting of updating the description section, position statement, dosage/administration, and references.
03/15/17	Review and revision to guideline consisting of removal of the age requirement in the position statement, and updates to description section, precautions section, and references.
02/15/18	Review and revision to guideline consisting of updates to description, position statement, dosage/administration, precautions, related guidelines, and references sections.
02/15/19	Review and revision to guideline consisting of updates to description, position statement, definitions, and references sections.