ponatinib (Iclusig®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO225

Description

Ponatinib (Iclusig) is an orally administered tyrosine kinase inhibitor with activity against unmutated and mutated BCR-ABL including the threonine-to-isoleucine mutation at position 315 (T315I).

Length of Authorization

- Initial: six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication*	Quantity Limit
ponatinib (Iclusig)	10 mg tablet	CP-CML with resistance or intolerance to two prior kinase inhibitors	30 tablets/30 days
	15 mg tablet	AP-CML, BP-CML, and Ph+ ALL for whom no other kinase inhibitors are indicated	30 tablets/30 days
	30 mg tablet	T315I-positive CML (any phase) or T315I-positive Ph+ ALL	30 tablets/30 days
	45 mg tablet	Newly diagnosed Ph+ ALL in combination with chemotherapy	30 tablets/30 days

*CML = chronic myeloid leukemia, CP = chronic phase, AP = accelerated phase, BP = blast phase, Ph+ = Philadelphia chromosome positive, ALL = acute lymphoblastic leukemia

Initial Evaluation

I. **Ponatinib (Iclusig)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   C. A diagnosis of one of the following:
      1. **Chronic Phase-Chronic Myeloid Leukemia (CP-CML); AND**
         i. Documented resistance, or intolerance to, <u>two</u> prior tyrosine kinase inhibitors (TKIs) (e.g., dasatinib (Sprycel), imatinib (Gleevec), nilotinib (Tasigna), bosutinib (Bosulif); **OR**
            a. Documented positive T315I mutation; **AND**
         ii. Medication will <u>not</u> be used in combination with any other oncology therapy; **OR**

2. **Accelerated Phase- Chronic Myeloid Leukemia (AP-CML), Blast Phase- Chronic Myeloid Leukemia (BP-CML), or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (Ph+ ALL); AND**
    i. Provider attestation that all other tyrosine kinase inhibitors (TKIs) (e.g., dasatinib (Sprycel), imatinib (Gleevec), nilotinib (Tasigna), bosutinib (Bosulif) used to treat Accelerated Phase- Chronic Myeloid Leukemia (AP-CML), Blast Phase- Chronic Myeloid Leukemia (BP-CML), or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (Ph+ALL) have been ineffective, not tolerated, contraindicated or not indicated; **OR**
        a. Documented positive T315I mutation; **AND**
    ii. Medication will not be used in combination with any other oncology therapy; **OR**
3. **Newly diagnosed Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (Ph+ ALL); AND**
    i. Medication will be used in combination with chemotherapy (e.g., vincristine, cytarabine, methotrexate, cyclophosphamide, doxorubicin, daunorubicin, etc.)

I. Ponatinib (Iclusig) is considered investigational when used for all other conditions, including but not limited to:
    A. Newly diagnosed chronic phase chronic myeloid leukemia (CP-CML)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If this applies, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Medication will not be used with any other oncology therapy; **OR**
- Medication will be used in combination with chemotherapy (e.g., vincristine, cytarabine, methotrexate, cyclophosphamide, doxorubicin, daunorubicin, etc.) in newly diagnosed Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (Ph+ ALL); **AND**

IV. Member has exhibited response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread.

Supporting Evidence

I. Ponatinib (Iclusig) is an oral tyrosine kinase inhibitor with activity against unmutated and mutated BCR-ABL, including the threonine-to-isoleucine mutation at position 315 (T315I), which is present in around 20% of patients with tyrosine kinase inhibitor-resistant disease.

II. Ponatinib (Iclusig) carries four FDA approved indications and is used in the treatment of patients with chronic phase (CP) chronic myeloid leukemia (CML) with resistance or intolerance to at least two prior kinase inhibitors, accelerated phase (AP) or blast phase (BP) CML, Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom no other kinase inhibitors are indicated, T315I-positive CML (chronic phase, accelerated phase, or blast phase) or T315I-positive Ph+ ALL, and newly diagnosed Ph+ ALL in combination with chemotherapy.

Chronic Myeloid Leukemia (CML) and Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL) Resistant or Intolerant to Prior TKI

III. The original FDA approval for ponatinib (Iclusig) took place in 2012 and was based on the PACE clinical trial which evaluated safety and efficacy of ponatinib (Iclusig). Post-marketing studies submitted to the FDA included a 5 year follow up PACE study and an ongoing OPTIC clinical trial, which informed of the optimal dosing in patients with CP-CML.

IV. The PACE clinical trial was an open label, single arm, phase II study in adult subjects with CML (all phases) or Ph+ ALL with resistance/intolerance to dasatinib or nilotinib, or development of T315I mutation after tyrosine kinase inhibitor (TKI) therapy. There were 270 subjects in CP-CML, 85 subjects in AP-CML, 62 subjects in BP-CML, and 62 subjects in Ph+ALL. These subjects were further randomized based on T315I mutation status. Nearly one-third of subjects (29%) had the T315I mutation. The primary efficacy endpoint of major cytogenic response (MCyR) by 12 months of treatment was met in 51% of those with resistance or intolerance to prior TKI therapy and in 70% of those with a positive T315I mutation status in the CP-CML cohort. In AP-CML, BP-CML, and Ph+ALL the primary endpoint was major hematologic response (MaHR) by 6 months of treatment which was met in 57% of those with prior resistance or intolerance to TKI therapy and in 50% of those with a positive T315I mutation status in the AP-CML cohort. MaHR was met in 35% of those with resistance or intolerance to prior TKI therapy and in 33% of those with a positive T315I mutation status in the BP-CML/Ph+ALL cohort.

V. The five-year follow up study of ponatinib (Iclusig) demonstrated a continued clinical benefit in patients with heavily treated CML or Ph+ALL. The types of adverse events reported were generally similar to those reported previously and included rash (47%), abdominal pain (46%), thrombocytopenia (46%), headache (43%), and constipation (41%). Dose related adverse events included cardiovascular, cerebrovascular, and peripheral vascular events. The cumulative incidence of arterial occlusive events (AOEs) was 25% in the overall population (serious AOEs, 20%) and 31% in the CP-CML population (serious AOEs, 26%); higher cumulative incidence in CP-CML correlates with the longer duration of treatment.

VI. OPTIC is an ongoing phase 2, open label, randomized, multicenter clinical trial evaluating response-based dosing regimens of ponatinib (Iclusig) with the aim of optimizing its efficacy and safety in patients with CP-CML who are resistant or intolerant to prior TKI therapy. Interim results at 21 months of follow up show benefit of ponatinib (Iclusig) in all three dosing regimens

studied (15 mg, 30 mg, and 45 mg), with the 45 mg starting dose showing greatest efficacy results. Thus far, the FDA has made recommendations to start with the 45 mg dose which could subsequently be titrated down to 15 mg upon achievement of <1% BCR-ABL1. Primary analysis will provide a refined understanding of the benefit: risk profile of three different starting doses of ponatinib (Iclusig).

Newly Diagnosed Positive Acute Lymphoblastic Leukemia (Ph+ ALL)

VII. The PhALLCON trial evaluated ponatinib in combination with reduced-intensity chemotherapy (n=154) in the treatment of newly diagnosed Ph+ ALL compared to imatinib with reduced-intensity chemotherapy (n=78) in a phase 3, open-label, global clinical trial randomized 2:1 (ponatinib: imatinib). Ponatinib was dosed 30 mg orally daily in combination with chemotherapy for 20 cycles. After completion of 20 cycles of chemotherapy, ponatinib monotherapy was continued at 30mg daily. Patients were able to decrease the dose to 15 mg orally daily based on MRD status after induction. Imatinib was dosed 600 mg orally daily for 20 cycles, followed by monotherapy thereafter. Patients did not have the option to reduce the dose of imatinib. The primary endpoint was MRD-negative complete remission at the end of induction (end of cycle 3). This was defined as investigator-reported complete remission for 4 weeks or longer and MRD-negativity defined as $\leq$ 0.01% BCR:ABL1/ABL1 molecular response (MR4). Ponatinib significantly achieved MRD-negative complete remission at the end of induction in 34.4% of patients compared to imatinib's 16.7% (risk difference, 0.18 [95% CI 0.06 – 0.29]; relative risk, 2.06 [95% CI 1.19 – 3.56]; p-value, 0.002). Secondary endpoints included event-free survival, progression-free survival, overall survival, MRD-negativity at the end of induction, and duration of MRD-negative complete remission. The only significant findings were progression-free survival (HR 0.58 [95% CI 0.41 – 0.83]) and those that achieved MRD-negativity at the end of induction (risk difference, 0.21 [95% CI 0.08 – 0.34]; relative risk, 1.94 [95% CI 1.19 – 3.17]; p-value, 0.002). The safety profiles for both ponatinib and imatinib were similar. The most common AEs experienced were ALT increase, hypertension, and decreased platelet, WBC, and neutrophils counts with 20 discontinuing ponatinib treatment and 10 discontinuing imatinib treatment due to adverse events. The adverse events weren't specified and overall, no deaths occurred due to treatment.

VIII. For the treatment of Ph+ ALL, current NCCN guidelines recommend TKIs such as bosutinib (Bosulif), dasatinib (Sprycel), imatinib (Gleevec), nilotinib (Tasigna), or ponatinib (Iclusig) as preferred agents. Imatinib use in first line should be restricted to patients who cannot tolerate broader acting TKIs. Not all TKIs have been studied directly within the context of each regimen proposed by NCCN. There is limited data for bosutinib (Bosulif) in Ph+ ALL. Moreover, certain TKIs are contraindicated with specific BCR-ABL1 mutations; ponatinib (Iclusig) is the only TKI without any contraindicated mutations.

IX. For the treatment of CP-CML, current NCCN guidelines recommend the following agents depending on the patient's risk score and mutation profile: imatinib (Gleevec), bosutinib (Bosulif), dasatinib (Sprycel), nilotinib (Tasigna) when there's resistance to two prior TKIs (category 2a). For the treatment of AP-CML and BP-CML, preferred regimens include bosutinib (Bosulif), dasatinib (Sprycel), nilotinib (Tasigna), or ponatinib (Iclusig). These agents are

preferred over imatinib (Gleevec). Imatinib (Gleevec) may be considered in patients with contraindications to other TKIs.

Investigational or Not Medically Necessary Uses

I. Ponatinib (Iclusig) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Newly diagnosed CP-CML
      i. Ponatinib (Iclusig) was studied as a first line agent in patients newly diagnosed with CP-CML and showed an increase in risk of serious adverse reactions 2-fold compared to imatinib (Gleevec) 400 mg once daily. This prospective randomized clinical trial was subsequently halted for safety. Ponatinib (Iclusig) treated patients exhibited a greater incidence of myelosuppression, pancreatitis, hepatotoxicity, cardiac failure, hypertension, and skin and subcutaneous tissue disorders. Ponatinib (Iclusig) is not indicated and is not recommended for the treatment of patients with newly diagnosed CP-CML.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
imatinib (Gleevec®)	Chronic eosinophilic leukemia
	Dermatofibrosarcoma protuberans, unresectable, recurrent, and/or metastatic
	Gastrointestinal stromal tumor, Kit (CD117)-positive, adjuvant treatment
	Gastrointestinal stromal tumor, Kit (CD117)-positive, unresectable or metastatic disease
	Hypereosinophilic syndrome
	Myelodysplastic syndrome, PDGFR gene rearrangement
	Myelodysplastic syndrome, chronic, PDGFR gene rearrangement
	Philadelphia chromosome-positive acute lymphoblastic leukemia, newly diagnosed, in combination with chemotherapy
	Philadelphia chromosome-positive acute lymphoblastic leukemia, relapsed/refractory
	Philadelphia chromosome positive chronic myelogenous leukemia, accelerated phase or blast crisis
	Philadelphia chromosome positive chronic myelogenous leukemia, chronic phase, after failure of interferon-alpha therapy
	Philadelphia chromosome positive chronic myelogenous leukemia, chronic phase, newly diagnosed

	Systemic mast cell disease, aggressive, D816V c-Kit mutation negative or unknown
dasatinib (SPRYCEL®)	Philadelphia chromosome-positive (Ph+) Chronic myeloid leukemia (CML)/ Ph+ Acute lymphoblastic leukemia (ALL)
	Chronic phase CML
	Gastrointestinal Stromal Tumors (GIST)
bosutinib (Bosulif®)	CML, newly diagnosed chronic phase
	CML, resistant or intolerant to prior therapy
nilotinib (Tasigna®; Danziten™)	Newly diagnosed OR resistant/intolerant Ph+ CML in chronic phase
	Newly diagnosed Ph+ CML in chronic phase
	Resistant or intolerant Ph+ CML Gastrointestinal Stromal Tumors (GIST)

References

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3. NCCN Guidelines. Acute Lymphoblastic Leukemia. Version 2.2024-July 19, 2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/all_blocks.pdf. Accessed on October 4, 2024.
4. Cortes, Jorge E et al. "Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial." Blood vol. 132,4 (2018): 393-404. doi:10.1182/blood-2016-09-739086
5. Cortes, Jorge E et al. "A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias." The New England journal of medicine vol. 369,19 (2013): 1783-96. doi:10.1056/NEJMoa1306494
6. Jabbour E, Kantarjian HM, Aldoss I, et al. Ponatinib vs Imatinib in Frontline Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: A Randomized Clinical Trial. *JAMA*. 2024;331(21):1814-1823. doi:10.1001/jama.2024.4783

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated initial approval period to 6 months. Updated policy criteria to reflect most up to date format. Added newly diagnosed Ph+ ALL indication with relevant supporting evidence. Added related policies table.	02/2025
Policy criteria transitioned to a new format; criteria changes include the removal of laboratory monitoring requirements (blood counts, hepatic enzyme tests, serum lipase) and monitoring of atrial thrombotic events, addition of a new dosage forms 10 mg and 30 mg tablets, and addition of requiring two prior TKIs in CP-CML, consistent with the FDA labeling change.	03/2021
Policy criteria created	05/2013