

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: three 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; AP-CML, BP-CML, and Ph+ ALL for whom no other kinase inhibitors are indicated; T315I-positive CML (any phase) or T315I-positive Ph+ ALL	30 tablets/30 days
	15 mg tablet		30 tablets/30 days
	30 mg tablet		30 tablets/30 days
	45 mg tablet		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. Medication is not used in combination with any other oncology therapy; **AND**
  - D. A diagnosis of **Chronic Phase-Chronic Myeloid Leukemia (CP-CML)**; **AND**
    1. Documented resistance, or intolerance to, two prior tyrosine kinase inhibitors (TKIs) (e.g., dasatinib (Sprycel), imatinib (Gleevec), nilotinib (Tasigna), bosutinib (Bosulif); **OR**
    2. Documented positive T315I mutation
  - E. A diagnosis of **Accelerated Phase- Chronic Myeloid Leukemia (AP-CML), Blast Phase-Chronic Myeloid Leukemia (BP-CML), or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (Ph+ALL)**; **AND**

1. Provider attestation that all other TKIs used to treat AP-CML, BP-CML, or Ph+ALL (e.g., dasatinib (Sprycel), imatinib (Gleevec), nilotinib (Tasigna), bosutinib (Bosulif) have been ineffective, not tolerated, contraindicated or not indicated; **OR**
  2. Documented positive T315I mutation
- I. Ponatinib (Iclusig) is considered investigational when used for all other conditions, including but not limited to:
- A. Newly diagnosed 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. Will not be used with any other oncology therapy; **AND**
- IV. Disease response to treatment defined by stabilization of disease or decrease in rate of disease progression.

### 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 three 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, and T315I-positive CML (chronic phase, accelerated phase, or blast phase) or T315I-positive Ph+ ALL.
- 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 cytogenetic 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).
- VII. For the treatment of Ph+ALL, current NCCN guidelines recommend dasatinib (Sprycel) and imatinib (Gleevec) as the preferred agents as well as other TKIs such as bosutinib (Bosulif), nilotinib (Tasigna), or ponatinib (Iclusig). Moreover, certain TKIs are contraindicated with specific BCR-ABL1 mutations; ponatinib (Iclusig) is the only TKI without any contraindicated mutations.
- VIII. 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), or ponatinib (Iclusig) when there's resistance to two prior TKIs. For the treatment of AP-CML and BP-CML, preferred regimens include bosutinib (Bosulif), dasatinib (Sprycel), nilotinib (Tasigna), or ponatinib (Iclusig) with omacetaxine (Synribo) cited as being useful in certain circumstances.

### 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.

### References

1. ICLUSIG (ponatinib) [package insert]. Cambridge, MA: ARIAD Pharmaceuticals, Inc.; December 2020.
2. NCCN Guidelines. Chronic Myeloid Leukemia. Version 3.2021-January 13, 2021. Available at: [https://www.nccn.org/professionals/physician\\_gls/pdf/cml\\_blocks.pdf](https://www.nccn.org/professionals/physician_gls/pdf/cml_blocks.pdf). Accessed on March 7, 2021.
3. NCCN Guidelines. Acute Lymphoblastic Leukemia. Version 2.2020-October 23, 2020. Available at: [https://www.nccn.org/professionals/physician\\_gls/pdf/all\\_blocks.pdf](https://www.nccn.org/professionals/physician_gls/pdf/all_blocks.pdf). Accessed on March 7, 2021.
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

### Policy Implementation/Update:

Action and Summary of Changes	Date
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