Evolent Clinical Guideline 3056 for Iclusig™ (ponatinib)

Guideline Number:	Applicable Codes	
Evolent_CG_3056		
"Evolent" refers to Evolent Health LLC and Evolent Specialty Services, Inc. *© 2013 - 2026 Evolent. All rights Reserved.*		
Original Date:	**Last Revised Date:**	**Implementation Date:**
May 2013	April 2026	April 2026

TABLE OF CONTENTS

STATEMENT **2**
PURPOSE 2
INDICATIONS **2**
ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) 2
CHRONIC MYELOID LEUKEMIA (CML) 2
CONTRAINDICATIONS/WARNINGS **3**
EXCLUSION CRITERIA **3**
CODING AND STANDARDS **4**
CODES 4
APPLICABLE LINES OF BUSINESS 4
POLICY HISTORY **5**
LEGAL AND COMPLIANCE **5**
GUIDELINE APPROVAL 5
Committee *5*
DISCLAIMER 5
REFERENCES **6**

STATEMENT

Purpose

To define and describe the accepted indications for Iclusig (ponatinib) usage in the treatment of cancer, including FDA approved indications, and off-label indications.

Evolent is responsible for processing all medication requests from network ordering providers. Medications not authorized by Evolent may be deemed as not approvable and therefore not reimbursable.

The use of this drug must be supported by one of the following: FDA approved product labeling, CMS-approved compendia, National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO) clinical guidelines, or peer-reviewed literature that meets the requirements of the CMS Medicare Benefit Policy Manual Chapter 15.

INDICATIONS

Continuation requests for a not-approvable medication shall be exempt from this Evolent policy provided

- The member has not experienced disease progression on the requested medication AND
- The requested medication was used within the last year without a lapse of more than 30 days of having an active authorization AND
- Additional medication(s) are not being added to the continuation request.

Acute Lymphoblastic Leukemia (ALL)

- Iclusig (ponatinib), in combination with chemotherapy, may be used in adult members with newly diagnosed Philadelphia chromosome/BCR-ABL positive ALL.
- The member has Philadelphia chromosome/BCR-ABL positive ALL and Iclusig (ponatinib) may be used as a single agent or in combination with chemotherapy if there is documented intolerance, contraindications, or disease progression on generic imatinib OR
- Iclusig (ponatinib) may be used as a single agent for members with T315I mutation positive Philadelphia chromosome/BCR-ABL positive ALL.

Chronic Myeloid Leukemia (CML)

- Iclusig (ponatinib) may be used as single agent for subsequent line therapy if there is documented intolerance, contraindications, or disease progression on generic imatinib and one other Tyrosine Kinase Inhibitor (TKI): Tasigna (nilotinib) or Sprycel (dasatinib) OR
- Iclusig (ponatinib) may be used as a single agent for members with T315I mutation

positive CML.

CONTRAINDICATIONS/WARNINGS

- Contraindications
  - None
- US Boxed Warning
  - Arterial occlusive events (AOEs), including fatalities, have occurred in ponatinib-treated patients. AOEs 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 50 years of age and younger, experienced these events. Monitor for evidence of AOEs. Interrupt or discontinue ponatinib based on severity. Consider benefit-risk to guide a decision to restart ponatinib.
  - Venous thromboembolic events (VTEs) have occurred in ponatinib-treated patients. Monitor for evidence of VTEs. Interrupt or discontinue ponatinib based on severity.
  - Heart failure, including fatalities, occurred in ponatinib-treated patients. Monitor for heart failure and manage patients as clinically indicated. Interrupt or discontinue ponatinib for new or worsening heart failure.
  - Hepatotoxicity, liver failure, and death have occurred in ponatinib-treated patients. Monitor liver function tests. Interrupt or discontinue ponatinib based on severity.

EXCLUSION CRITERIA

- Disease progression while taking Iclusig (ponatinib).
- Use of Iclusig (ponatinib) for the treatment of members with newly diagnosed CML without the T315I mutation.
- Concurrent use with other anticancer therapies for the treatment of CML.
- Use of Iclusig (ponatinib) in Philadelphia chromosome/BCR-ABL negative ALL or T315I mutation negative ALL (if used as monotherapy) or CML.
- Dosing exceeds single dose limit of Iclusig (ponatinib) 45 mg.
- Treatment exceeds the maximum limit of 30 (10 mg), 30 (15 mg), 30 (30 mg), or 30 (45 mg) tablets/month.
- Investigational use of Iclusig (ponatinib) with an off-label indication that is not sufficient in evidence or is not generally accepted by the medical community. Sufficient evidence that is not supported by CMS recognized compendia or acceptable peer reviewed literature is defined as any of the following:
  - Whether the clinical characteristics of the patient and the cancer are adequately represented in the published evidence.

- Whether the administered chemotherapy/biologic therapy/immune therapy/targeted therapy/other oncologic therapy regimen is adequately represented in the published evidence.
- Whether the reported study outcomes represent clinically meaningful outcomes experienced by patients. Generally, the definitions of Clinically Meaningful outcomes are those recommended by ASCO, e.g., Hazard Ratio of less than 0.80 and the recommended survival benefit for OS and PFS should be at least 3 months.
- Whether the experimental design, considering the drugs and conditions under investigation, is appropriate to address the investigative question. (For example, in some clinical studies, it may be unnecessary or not feasible to use randomization, double blind trials, placebos, or crossover).
- That non-randomized clinical trials with a significant number of subjects may be a basis for supportive clinical evidence for determining accepted uses of drugs.
- That case reports are generally considered uncontrolled and anecdotal information and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.
- That abstracts (including meeting abstracts) without the full article from the approved peer-reviewed journals lack supporting clinical evidence for determining accepted uses of drugs.

CODING AND STANDARDS

Codes

- J8999 - ponatinib

Applicable Lines of Business

☐	CHIP (Children's Health Insurance Program)
☒	Commercial
☒	Exchange/Marketplace
☒	Medicaid
☐	Medicare Advantage

POLICY HISTORY

Date	Summary
April 2026	• Updated references
April 2025	• Converted to new Evolent guideline template • This guideline replaces UM ONC_1241 Iclusig (ponatinib) • Updated maximum dosage form quantities in exclusion criteria • Updated references
April 2024	• Updated ALL indication section to include use with chemotherapy for adult members with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) • Updated NCH verbiage to Evolent • Updated exclusion criteria • Added new reference

LEGAL AND COMPLIANCE

Guideline Approval

Committee

Reviewed / Approved by Evolent Specialty Services Clinical Guideline Review Committee

Disclaimer

Evolent Clinical Guidelines do not constitute medical advice. Treating health care professionals are solely responsible for diagnosis, treatment, and medical advice. Evolent uses Clinical Guidelines in accordance with its contractual obligations to provide utilization management. Coverage for services varies for individual members according to the terms of their health care coverage or government program. Individual members' health care coverage may not utilize some Evolent Clinical Guidelines. Evolent clinical guidelines contain guidance that requires prior authorization and service limitations. A list of procedure codes, services or drugs may not be all inclusive and does not imply that a service or drug is a covered or non-covered service or drug. Evolent reserves the right to review and update this Clinical Guideline in its sole discretion. Notice of any changes shall be provided as required by applicable provider agreements and laws or regulations. Members should contact their Plan customer service representative for specific coverage information.

REFERENCES

1. Jabbour E, et al. Ponatinib vs Imatinib in Frontline Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: A Randomized Clinical Trial. *JAMA*. 2024 Jun 4;331(21):1814-1823. doi: 10.1001/jama.2024.4783.
2. Jabbour E, et al. S110: PHALLCON: A PHASE 3 STUDY COMPARING PONATINIB VERSUS IMATINIB IN NEWLY DIAGNOSED PH+ ALL. *Hemasphere*. 2023 Aug 8;7(Suppl):e68516d0. doi: 10.1097/01.HS9.0000967352.68516.d0.
3. Cortes J, et al. Ponatinib dose-ranging study in chronic-phase chronic myeloid leukemia: a randomized, open-label phase 2 clinical trial. *Blood*. 2021 Nov 25;138(21):2042-2050. doi: 10.1182/blood.2021012082.
4. Cortes JE, et al. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial. *Blood*. 2018 Jul 26;132(4):393-404. doi: 10.1182/blood-2016-09-739086.
5. Iclusig prescribing information. Takeda Pharmaceuticals America, Inc. Cambridge, MA 2025.
6. Clinical Pharmacology Elsevier Gold Standard 2026.
7. Micromedex® Healthcare Series: Micromedex Drugdex Ann Arbor, Michigan 2026.
8. National Comprehensive Cancer Network. Cancer Guidelines and Drugs and Biologics Compendium 2026.
9. AHFS Drug Information. American Society of Health-Systems Pharmacists or Wolters Kluwer Lexi-Drugs. Bethesda, MD 2026.
10. Ellis LM, et al. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. *J Clin Oncol*. 2014 Apr 20;32(12):1277-80.
11. Medicare Benefit Policy Manual Chapter 15 Covered Medical and Other Health Services: https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/bp102c15.pdf.
12. Current and Resolved Drug Shortages and Discontinuations Reported to the FDA: http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm.