PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Iclusig Prior Authorization Policy
- Iclusig® (ponatinib tablets – ARIAD/Takeda)

REVIEW DATE: 03/26/2025; selected revision 05/14/2025

INSTRUCTIONS FOR USE

THE FOLLOWING COVERAGE POLICY APPLIES TO HEALTH BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. CERTAIN CIGNA COMPANIES AND/OR LINES OF BUSINESS ONLY PROVIDE UTILIZATION REVIEW SERVICES TO CLIENTS AND DO NOT MAKE COVERAGE DETERMINATIONS. REFERENCES TO STANDARD BENEFIT PLAN LANGUAGE AND COVERAGE DETERMINATIONS DO NOT APPLY TO THOSE CLIENTS. COVERAGE POLICIES ARE INTENDED TO PROVIDE GUIDANCE IN INTERPRETING CERTAIN STANDARD BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. PLEASE NOTE, THE TERMS OF A CUSTOMER'S PARTICULAR BENEFIT PLAN DOCUMENT [GROUP SERVICE AGREEMENT, EVIDENCE OF COVERAGE, CERTIFICATE OF COVERAGE, SUMMARY PLAN DESCRIPTION (SPD) OR SIMILAR PLAN DOCUMENT] MAY DIFFER SIGNIFICANTLY FROM THE STANDARD BENEFIT PLANS UPON WHICH THESE COVERAGE POLICIES ARE BASED. FOR EXAMPLE, A CUSTOMER'S BENEFIT PLAN DOCUMENT MAY CONTAIN A SPECIFIC EXCLUSION RELATED TO A TOPIC ADDRESSED IN A COVERAGE POLICY. IN THE EVENT OF A CONFLICT, A CUSTOMER'S BENEFIT PLAN DOCUMENT ALWAYS SUPERSEDES THE INFORMATION IN THE COVERAGE POLICIES. IN THE ABSENCE OF A CONTROLLING FEDERAL OR STATE COVERAGE MANDATE, BENEFITS ARE ULTIMATELY DETERMINED BY THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT. COVERAGE DETERMINATIONS IN EACH SPECIFIC INSTANCE REQUIRE CONSIDERATION OF 1) THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT IN EFFECT ON THE DATE OF SERVICE; 2) ANY APPLICABLE LAWS/REGULATIONS; 3) ANY RELEVANT COLLATERAL SOURCE MATERIALS INCLUDING COVERAGE POLICIES AND; 4) THE SPECIFIC FACTS OF THE PARTICULAR SITUATION. EACH COVERAGE REQUEST SHOULD BE REVIEWED ON ITS OWN MERITS. MEDICAL DIRECTORS ARE EXPECTED TO EXERCISE CLINICAL JUDGMENT WHERE APPROPRIATE AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. WHERE COVERAGE FOR CARE OR SERVICES DOES NOT DEPEND ON SPECIFIC CIRCUMSTANCES, REIMBURSEMENT WILL ONLY BE PROVIDED IF A REQUESTED SERVICE(S) IS SUBMITTED IN ACCORDANCE WITH THE RELEVANT CRITERIA OUTLINED IN THE APPLICABLE COVERAGE POLICY, INCLUDING COVERED DIAGNOSIS AND/OR PROCEDURE CODE(S). REIMBURSEMENT IS NOT ALLOWED FOR SERVICES WHEN BILLED FOR CONDITIONS OR DIAGNOSES THAT ARE NOT COVERED UNDER THIS COVERAGE POLICY (SEE "CODING INFORMATION" BELOW). WHEN BILLING, PROVIDERS MUST USE THE MOST APPROPRIATE CODES AS OF THE EFFECTIVE DATE OF THE SUBMISSION. CLAIMS SUBMITTED FOR SERVICES THAT ARE NOT ACCOMPANIED BY COVERED CODE(S) UNDER THE APPLICABLE COVERAGE POLICY WILL BE DENIED AS NOT COVERED. COVERAGE POLICIES RELATE EXCLUSIVELY TO THE ADMINISTRATION OF HEALTH BENEFIT PLANS. COVERAGE POLICIES ARE NOT RECOMMENDATIONS FOR TREATMENT AND SHOULD NEVER BE USED AS TREATMENT GUIDELINES. IN CERTAIN MARKETS, DELEGATED VENDOR GUIDELINES MAY BE USED TO SUPPORT MEDICAL NECESSITY AND OTHER COVERAGE DETERMINATIONS.

CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Iclusig, a tyrosine kinase inhibitor (TKI), is indicated for the following uses in adults:[1]

- **Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL):**
  - Newly diagnosed, in combination with chemotherapy.
  - For whom no other TKIs are indicated as monotherapy.
  - T315I-positive, as monotherapy.
- **Chronic myeloid leukemia (CML):**
  - Chronic phase, with resistance or intolerance to at least two prior TKIs.
  - Accelerated phase or blast phase for whom no other kinase inhibitors are indicated.
  - T315I-positive (chronic phase, accelerated phase, or blast phase).

A limitation of use is that Iclusig is not indicated and is not recommended for the treatment of patients with newly diagnosed chronic phase CML.[1]

The indication of Ph+ ALL in newly diagnosed patients in combination with chemotherapy is approved under accelerated approval based on minimal residual disease (MRD)-negative complete remission (CR) at the end of induction. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial(s).[1]

Guidelines

Iclusig is addressed in guidelines from National Comprehensive Cancer Network (NCCN):[2-4]

- **ALL:** NCCN guidelines (version 3.2024 – December 20, 2024) [adults and adolescent young adults] recommend Iclusig as a treatment option for patients with the T315I mutation and/or for patients for whom no other TKI is indicated (category 2A).[2] Iclusig is also recommended in combination with various regimens used for induction or consolidation therapy for Ph+ ALL during frontline therapy or for relapsed/refractory therapy if not previously given (category 2A). NCCN guidelines for pediatric ALL (version 3.2025 – March 17, 2024) recommend Iclusig for relapsed or refractory *BCR:: ABL1*-positive ALL (category 2B) and for relapsed/refractory T cell-ALL with *ABL*-class translocation (category 2A).[3]
- **CML:** NCCN guidelines (version 3.2025 – November 27, 2024) recommend Iclusig as an option for patients with Ph+ or *BCR::ABL1*-positive disease and a T315I mutation and/or chronic phase CML with resistance or intolerance to at least two prior TKIs. Iclusig is also recommended for patients with accelerated-phase CML or blast-phase CML for whom no other TKI is indicated (category 2A).[4] The guidelines recommend to switch to Iclusig as alternate TKI treatment in patients with chronic phase CML (chronic phase-CML) with a T315I mutation, or with no identifiable *BCR::ABL1* mutations (preferred), or for patients resistant or intolerant to ≥ 2 TKIs for *BCR::ABL1* transcript levels (category 2A).
- **Gastrointestinal Stromal Tumor (GIST)**: NCCN guidelines (version 2.2024 – July 31, 2024) recommend Iclusig as "Useful in Certain Circumstances" after progression on approved therapies (category 2A); the guidelines state that Iclusig has demonstrated activity in advanced GIST, particularly in patients with *KIT* exon 11 mutant disease.[5] Imatinib is a preferred regimen for first-line therapy (category 1) for sensitive mutations (excluding platelet-derived growth factor receptor alpha [*PDGFRA]* exon 18 mutations that are insensitive to imatinib including D842V mutation). Ayvakit® (avapritinib tablets) is also a preferred regimen (category 2A) for GIST with *PDGFRA* exon 18 mutations that are insensitive to imatinib, including the *PDGFRA* D842V mutation. Second-line therapies include sunitinib as "preferred" (category 1) and dasatinib as "other recommended regimen" (category 2A). Stivarga® (regorafenib tablets) is a "preferred" third-line therapy (category 1). Qinlock® (ripretinib tablets) is a "preferred" fourth-line therapy (category 1).
- **Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions:** NCCN guidelines (version 1.2025 – February 21, 2025) recommend Iclusig for *ABL1* and *FGFR1* rearrangements in chronic phase or blast phase as "Other Recommended Regimens" (category 2A).[6] It is also recommended as treatment in combination with ALL- or acute myeloid

leukemia-type induction chemotherapy followed by allogeneic hematopoietic stem cell transplantation (HSCT) [if eligible] for lymphoid, myeloid or mixed lineage neoplasms with eosinophilia and *ABL1* and *FGFR1* rearrangements in blast phase (category 2A).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Iclusig. All approvals are provided for the duration noted below.

- **Iclusig® (ponatinib tablets (ARIAD/Takeda)**

is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

FDA-Approved Indications

1. **Acute Lymphoblastic Leukemia.** Approve for 1 year if the patient meets BOTH of the following (A, and B):
   - **A)** Patient meets ONE of the following (i or ii):
     - **i.** Patient has Philadelphia chromosome-positive acute lymphoblastic leukemia; OR
     - **ii.** Patient has *ABL*-class translocation; AND
   - **B)** Patient meets ONE of the following (i, ii, or iii):
     - **i.** The medication will be used in combination with chemotherapy; OR
     - **ii.** The acute lymphoblastic leukemia is T315I-positive; OR
     - **iii.** Patient has tried at least one other tyrosine kinase inhibitor.
       Note: Examples include imatinib and dasatinib.

2. **Chronic Myeloid Leukemia (CML).** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient meets ONE of the following (i or ii):
     - **i.** Patient has Philadelphia chromosome-positive chronic myeloid leukemia; OR
     - **ii.** Patient has *BCR::ABL1*- positive chronic myeloid leukemia; AND
   - **C)** Patient meets ONE of the following (i, ii or iii):
     - **i.** The chronic myeloid leukemia is T315I-positive, OR
     - **ii.** Patient has tried at least one other tyrosine kinase inhibitors; OR
       Note: Examples of tyrosine kinase inhibitors include imatinib, dasatinib, Danziten (nilotinib tablets), Tasigna (nilotinib capsules), and Nilotinib capsules.
     - **iii.** Patient meets BOTH of the following (a and b):
       - **a)** Patient has accelerated-phase CML or blast-phase CML; AND
       - **b)** No other tyrosine kinase inhibitor is indicated.

Other Uses with Supportive Evidence

3. **Gastrointestinal Stromal Tumor.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has tried each of the following (i, ii, iii, and iv):
      i. One of imatinib or Ayvakit (avapritinib tablets); AND
      ii. One of sunitinib or dasatinib; AND
      iii. Stivarga (regorafenib tablets); AND
      iv. Qinlock (ripretinib tablets).

4. **Myeloid/Lymphoid Neoplasms with Eosinophilia.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient meets ONE of the following (i or ii):
      i. The tumor has an *ABL1* rearrangement; OR
      ii. The tumor has an *FGFR1* rearrangement.

CONDITIONS NOT COVERED

- **Iclusig® (ponatinib tablets (ARIAD/Takeda)**

is(are) considered not medically necessary for ANY other use(s); criteria will be updated as new published data are available.

REFERENCES

1. Iclusig® tablets [prescribing information]. Lexington, MA: ARIAD/Takeda; March 2024.
2. The NCCN Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (version 3.2024 – December 20, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 17, 2025.
3. The NCCN Pediatric Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (version 3.2025 – March 17, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 17, 2025.
4. The NCCN Chronic Myeloid Leukemia Clinical Practice Guidelines in Oncology (version 3.2025 – November 27, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 17, 2025.
5. The NCCN Gastrointestinal Stromal Tumors Guidelines in Oncology (version 2.2024 – July 31, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 17, 2025.
6. The NCCN Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions Clinical Practice Guidelines in Oncology (version 1.2025 – February 21, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 17, 2025.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Chronic Myeloid Leukemia (CML):** Criteria were added for a patient who has accelerated-phase CML or blast-phase CML and no other tyrosine kinase inhibitor is indicated. **Gastrointestinal Stromal Tumor:** This new condition of approval was added to "Other Uses With Supportive Evidence" section based on	05/31/2023

	National Comprehensive Cancer Network (NCCN) guideline recommendations.	
Early Annual Revision	**Acute Lymphoblastic Leukemia (ALL):** An option for approval was added which states that the medication will be used in combination with chemotherapy. This is based on new FDA labeled indication in newly diagnosed Philadelphia chromosome-positive ALL in combination with chemotherapy.	03/27/2024
Selected Revision	**Acute Lymphoblastic Leukemia:** The age requirement was changed from ≥18 years of age to ≥ 15 years of age. The requirement that the patient has tried "two" other tyrosine kinase inhibitors that are used for Philadelphia chromosome-positive acute lymphoblastic leukemia was changed to at least "one" other tyrosine kinase inhibitor that is used for Philadelphia chromosome-positive acute lymphoblastic leukemia.	06/05/2024
Annual Revision	**Acute Lymphoblastic Leukemia:** The requirement that patient is ≥ 15 years of age was removed. The following option for approval was added "patient has *ABL*-class translocation." The following wording "…that is used for Philadelphia chromosome positive acute lymphoblastic leukemia" was removed from the requirement of trial of at least one other tyrosine kinase inhibitor. Brand names Sprycel and Phyrago was removed from the note of examples of tyrosine kinase inhibitors. **Chronic Myeloid Leukemia:** The following option for approval was added, "patient has *BCR::ABL1*-positive chronic myeloid leukemia." The following wording "…indicated for use in Philadelphia chromosome positive chronic myeloid leukemia" was removed from the requirement of trial of at least two other tyrosine kinase inhibitor. Danziten (nilotinib tablets) and Nilotinib capsules were added to the note with examples of tyrosine kinase inhibitors and brand names Sprycel and Phyrago were removed.	03/26/2025
Selected Revision	**Chronic Myeloid Leukemia:** The option for approval which states that patient has tried at least "two other tyrosine kinase inhibitors" was changed to "one other tyrosine kinase inhibitor."	05/14/2025