Clinical Policy: Ponatinib (Iclusig)

Reference Number: CP.PHAR.112
Effective Date: 06.01.13
Last Review Date: 05.24
Line of Business: Commercial, HIM, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Ponatinib (Iclusig®) is a kinase inhibitor.

FDA Approved Indication(s)

Iclusig is indicated for the treatment of adult patients with:

- Chronic phase chronic myeloid leukemia (CML) with resistance or intolerance to at least two prior kinase inhibitors.
- Accelerated phase, or blast phase chronic myeloid leukemia (CML) or as monotherapy in Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated.
- T315I-positive CML (chronic phase, accelerated phase, or blast phase) or as monotherapy in T315I-positive Ph+ ALL.
- Newly diagnosed Ph+ ALL, in combination with chemotherapy. This indication 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).

Limitation(s) of use: Iclusig is not indicated and is not recommended for the treatment of patients with newly diagnosed chronic phase CML.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Iclusig is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Chronic Myeloid Leukemia (must meet all):

1. Diagnosis of Ph+ (BCR-ABL1-positive) CML;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Member meets one of the following (a, b or c):
   a. Request is for chronic phase CML and member has experienced resistance, toxicity, or intolerance to prior therapy with two or more TKIs (e.g., imatinib, Bosulif®, Sprycel®, Tasigna®);

b. Request is for accelerated or blast phase CML for members whom no other TKI therapy is indicated;
c. Member has BCR-ABL T315I mutation;

5. For brand Iclusig requests, member must use generic ponatinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
6. Request meets one of the following (a or b):*
   a. Dose does not exceed 45 mg per day (one tablet per day);
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM - 6 months
Commercial - 12 months or duration of request, whichever is less

B. Acute Lymphoblastic Leukemia (must meet all):

1. Diagnosis of Ph+ (BCR-ABL1-positive) ALL;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Member meets one of the following (a, b, or c):
   a. Member has BCR-ABL T315I mutation;
   b. No other TKI therapy is indicated (e.g., imatinib, Bosulif, Sprycel, Tasigna);
   c. Member has newly diagnosed ALL, and request is for use in combination with chemotherapy (e.g., cyclophosphamide, vincristine, doxorubicin, daunorubicin, cytarabine, methotrexate);
5. For brand Iclusig requests, member must use generic ponatinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
6. Request meets one of the following (a or b):*
   a. Dose does not exceed one of the following (i or ii):
      i. One of the following (1 or 2):
         1) For newly diagnosed ALL as combination therapy: 30 mg per day;
         2) For all other requests: 45 mg per day;
      ii. One tablet per day;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM - 6 months
Commercial - 12 months or duration of request, whichever is less

C. Myeloid/Lymphoid Neoplasms (off-label) (must meet all)**:**

1. Diagnosis of lymphoid, myeloid or mixed lineage neoplasms with eosinophilia and FGFR1 or ABL1 rearrangement in blast or chronic phase;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. If disease is ABL1 rearrangement positive, one of the following (a or b):
   a. Member has contraindication, intolerance, or disease progression on imatinib;

b. Request is for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings *(see Appendix E)*;

5. For brand Iclusig requests, member must use generic ponatinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
6. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).*
   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM - 6 months
Commercial - 12 months or duration of request, whichever is less

D. Gastrointestinal Stromal Tumors (off-label) (must meet all)**:**
1. Diagnosis of gastrointestinal stromal tumor (GIST, a soft tissue sarcoma);
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Failure of imatinib, Qinlock™, Sutent®, or Stivarga® unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization may be required.*
5. Prescribed as a single agent;
6. For brand Iclusig requests, member must use generic ponatinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
7. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).*
   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM - 6 months
Commercial - 12 months or duration of request, whichever is less

E. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Iclusig for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. For brand Iclusig requests, member must use generic ponatinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
4. If request is for a dose increase, request meets one of the following (a or b):*
   a. New dose does not exceed one of the following (i or ii):
      i. One of the following (1 or 2):
         1) For newly diagnosed ALL as combination therapy: 30 mg per day;
         2) For all other requests: 45 mg per day;
      ii. One tablet per day;
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM – 12 months
Commercial – 12 months or duration of request, whichever is less

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ALL: acute lymphoblastic leukemia
CML: chronic myelogenous leukemia
FDA: Food and Drug Administration
TKI: tyrosine kinase inhibitor
Ph+: Philadelphia chromosome-positive

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose

imatinib (Gleevec®)	ALL:
	• Adult: 600 mg/day PO for relapsed / refractory Ph+ ALL
	• Pediatric: 340 mg/m^2/day PO in combination with chemotherapy for newly diagnosed Ph+ ALL
	CML:
	• Adult:
	  ○ 400-600 mg/day PO for chronic phase
	  ○ 600-800 mg/day PO for accelerated phase or blast crisis (800 mg given as 400 BID)
	• Pediatric: 340 mg/m^2/day PO for chronic phase
	
	MLNE: 100-400 mg PO QD [NCCN]
	GIST: 400 mg PO QD to 800 PO BID
		800 mg/day

Bosulif® (bosutinib)	400 mg PO QD	600 mg/day
Sprycel® (dasatinib)	Adults: • Chronic phase: 100-140 mg/day PO • Accelerated, myeloid phase, or lymphoid blast phase: 140-180 mg/day PO	Adults: 180 mg/day
Tasigna® (nilotinib)	Adults: 300 mg PO BID	Adults: 600 mg/day
Sutent (sunitinib)	GIST: 50 mg PO QD	50 mg/day
Stivarga (regorafenib)	GIST: 160 mg PO QD for the first 21 days of each 28-day cycle	160 mg/day
Quinlock (ripretinib)	GIST: 150 mg PO QD	150 mg/day

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): none reported
- Boxed warning(s): arterial occlusion, venous thromboembolism, heart failure, hepatotoxicity

Appendix D: General Information

- For newly diagnosed Ph+ ALL, the recommended dosage in the prescribing information for Iclusig states that Iclusig in combination with chemotherapy be continued for up to 20 cycles until loss of response or unacceptable toxicity. NCCN guidelines in ALL state that optimal duration of TKI when added to a maintenance regimen is unknown and does not include any recommendation for a maximum number of cycles for TKI combination therapy.

Appendix E: States with Regulations against Redirections in Certain Oncology Settings

State	Step Therapy Prohibited?	Notes
FL	Yes	For stage 4 metastatic cancer and associated conditions.
GA	Yes	For stage 4 metastatic cancer. Redirection does not refer to review of medical necessity or clinical appropriateness.
IA	Yes	For standard of care stage 4 cancer drug use, supported by peer-reviewed, evidence-based literature, and approved by FDA.
LA	Yes	For stage 4 advanced, metastatic cancer or associated conditions. Exception if "clinically equivalent therapy, contains identical active ingredient(s), and proven to have same efficacy.
MS	Yes	**Applies to HIM requests only** For advanced metastatic cancer and associated conditions
NV	Yes	Stage 3 and stage 4 cancer patients for a prescription drug to treat the cancer or any symptom thereof of the covered person
OH	Yes	**Applies to Commercial and HIM requests only** For stage 4 metastatic cancer and associated conditions
OK	Yes	**Applies to HIM requests only** For advanced metastatic cancer and associated conditions
PA	Yes	For stage 4 advanced, metastatic cancer
TN	Yes	For advanced metastatic cancer and associated conditions
TX	Yes	For stage 4 advanced, metastatic cancer and associated conditions

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Accelerated or blast phase CML and Ph+ ALL (monotherapy or T315I-positive)	Starting dose 45 mg PO QD. Consider reducing the dose of Iclusig for patients with accelerated phase (AP) CML who have achieved a major cytogenetic response.	45 mg/day
Chronic phase CML	Starting dosage is 45 mg PO QD with a reduction to 15 mg PO QD upon achievement of ≤1% BCR-ABL1. Patients	45 mg/day

Indication	Dosing Regimen	Maximum Dose
	with loss of response can re-escalate the dose of Iclusig to a previously tolerated dosage of 30 mg or 45 mg PO QD.	
Newly diagnosed Ph+ ALL	Starting dose is 30 mg PO QD in combination with chemotherapy, with a reduction to 15 mg PO QD upon achievement of MRD-negative (≤ 0.01% BCR::ABL1/ABL1) complete remission at the end of induction	30 mg/day

VI. Product Availability

Tablets: 10 mg, 15 mg, 30 mg, 45 mg

VII. References

1. Iclusig Prescribing Information. Cambridge, MA: Ariad Pharmaceuticals, Inc.; March 2024. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/203469s037lbl.pdf. Accessed March 27, 2024.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed January 11, 2024.
3. National Comprehensive Cancer Network Guidelines. Chronic Myeloid Leukemia Version 2.2024. Available at https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf. Accessed January 11, 2024.
4. National Comprehensive Cancer Network Guidelines. Acute Lymphoblastic Leukemia Version 4.2023. Available at https://www.nccn.org/professionals/physician_gls/pdf/all.pdf. Accessed March 27, 2024.
5. National Comprehensive Cancer Network Guidelines. Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes Version 1.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/mlne.pdf. Accessed January 11, 2024.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
2Q 2020 annual review: HIM line of business added; references reviewed and updated.	02.11.20	05.20
2Q 2021 annual review: added, Member has experienced resistance, toxicity, or intolerance to prior therapy with two or more TKIs (e.g., imatinib, bosutinib, dasatinib, nilotinib, ponatinib) for CML and ALL; allowed option for T315I mutation to bypass prior TKIs for CML; updated reference for HIM off-label use to HIM.PA.154 (replaces HIM.PHAR.21); references reviewed and updated.	02.12.21	05.21
2Q 2022 annual review: modified commercial approval duration from length of benefit to "12 months or duration of request, whichever is less"; WCG.CP.PHAR.112 to be retired and approval durations consolidated to 6 months initial and 12 months for continuation of therapy; added generic oral oncology redirection if available language;	01.31.22	05.22

Reviews, Revisions, and Approvals	Date	P&T Approval Date
per NCCN for CML clarified 2TKI requirement is for chronic phase CML and added additional option for accelerated or blast phase CML for members whom no other TKI therapy is indicated, for ALL removed 2 TKI requirement and replaced with requirement that either member has BCR-ABL T315I mutation or no other TKI therapy is indicated, added off-label criteria set for lymphoid, myeloid or mixed lineage neoplasms with redirection to imatinib for ABL1 rearrangement positive unless state regulations do not allow step therapy in certain oncology settings; added additional 10 mg and 30 mg strengths to Section VI; references reviewed and updated.		
Template changes applied to other diagnoses/indications.	09.30.22	
2Q 2023 annual review: for ALL added age requirement of 18 years or older, clarified HIM approval durations to be consistent with Medicaid line of business; references reviewed and updated.	01.06.23	05.23
2Q 2024 annual review: added criteria set for off-label use in gastrointestinal stromal tumor per NCCN Compendium; added quantity limit of one tablet per day; for Appendix B, removed Iclusig; for Appendix E, added state OK and updated state OH notes to include Commercial line of business; references reviewed and updated. RT4: added new indication and dosing for newly diagnosed Ph+ ALL per updated prescribing information.Revised Appendix D to E; in Appendix D added general information regarding the number of recommended cycles for combination therapy in newly diagnosed ALL.	03.27.24	05.24
Updated Appendix E to include Mississippi.	06.05.24	

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage

decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.