Iclusig® (ponatinib)
(Oral)

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I. Length of Authorization

Coverage will be provided for 6 months and may be renewed.

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Iclusig 10 mg tablet: 1 tablet per day
- Iclusig 15 mg tablet: 2 tablets per day
- Iclusig 30 mg tablet: 1 tablet per day
- Iclusig 45 mg tablet: 1 tablet per day

B. Max Units (per dose and over time) [HCPCS Unit]:

- 45 mg daily

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

- Patient is at least 18 years of age unless otherwise specified; **AND**

Universal Criteria [1]

- Patient has had a comprehensive baseline eye exam prior to initiating treatment and will receive periodic monitoring while on treatment; **AND**
- Patient will avoid concomitant therapy with all of the following, or if therapy is unavoidable, the patient will be monitored closely for adverse reaction and/or dose modifications will be implemented:
  - Coadministration with strong CYP3A inducers (e.g., rifampin, carbamazepine, St. John's Wort, etc.); **AND**
  - Coadministration with strong CYP3A inhibitors (e.g., itraconazole, ketoconazole, clarithromycin, etc.); **AND**
- Patient must not have had a surgical procedure within the preceding 14 days or have a surgical wound that has not fully healed; **AND**

Acute Lymphoblastic Leukemia (ALL) † Φ [1,2,4]

- Patient has Philadelphia chromosome-positive (Ph+) disease; **AND**
  - Disease is T315I mutation positive †; **OR**
  - Used in patients for whom no other tyrosine kinase inhibitor (TKI) is indicated †; **OR**
  - Used as maintenance therapy; **AND**
    - Used in combination with vincristine and prednisone with or without methotrexate and mercaptopurine for negative minimal residual disease after complete response to induction therapy; **OR**
    - Used as a single agent; **AND**
      - Used post-hematopoietic stem cell transplant; **OR**
      - Used in patients unfit for additional therapies; **OR**
  - Used as consolidation therapy; **AND**
    - Used for negative minimal residual disease after complete response to induction therapy; **AND**
      - Used as a single agent therapy in patients unfit for additional therapies; **OR**
      - Used combination with combination with blinatumomab for patients who are not candidates for multi-agent chemotherapy; **OR**
    - Used for persistent/rising minimal residual disease following a complete response to induction therapy; **AND**
      - Used in combination with blinatumomab; **OR**
      - Used as a single agent for patients who are unfit for additional therapies; **OR**
  - Patient is at least 15 years of age OR < 65 years of age without substantial comorbidities; **AND**
    - Used in a multiagent chemotherapy regimen for induction or consolidation therapy; **OR**
    - Used in combination with a corticosteroid for induction therapy; **OR**
    - Used in combination with vincristine and dexamethasone for induction therapy; **OR**
  - Patient is ≥ 65 years of age OR with substantial comorbidities; **AND**
    - Used as induction therapy as part of one of the following regimens:
      - As a single agent or in combination with a corticosteroid; **OR**
      - In combination with vincristine and dexamethasone; **OR**
      - In combination with a multiagent chemotherapy regimen; **OR**
  - Patient has relapsed/refractory disease; **AND**
    - Used as single agent therapy; **OR**
    - Used in combination with an induction therapy not previously used; **OR**
    - Used in combination with inotuzumab ozogamicin; **OR**
    - Used in combination with blinatumomab

Chronic Myeloid Leukemia (CML) † Φ [1,3,4]

- Patient's disease is confirmed by a *BCR-ABL1* positive laboratory test result; **AND**
- Patient does not have newly diagnosed chronic phase CML; **AND**
    - Patient has chronic, accelerated, or blast phase disease †; **AND**
        - Disease is T315I mutation positive †; **OR**
    - Patient chronic phase disease that is resistant or intolerant to prior therapy with at least two prior tyrosine kinase inhibitors (TKI) (e.g., imatinib, dasatinib, bosutinib, nilotinib, etc.) †; **OR**
    - Patient has accelerated or blast phase disease in which no other TKI is indicated †; **OR**
    - Used as switch therapy ‡; **AND**
        - Patient received initial therapy with one of the following: imatinib, bosutinib, dasatinib, or nilotinib; **AND**
        - Patient has *BCR-ABL1* transcript levels:
            - > 1% to 10% at 12 months; **OR**
            - > 10% at any response milestone

Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes ‡ [4,7]

- Patient has eosinophilia and FGFR1 or ABL1 rearrangements; **AND**
    - Patient has chronic or blast phase myeloid or lymphoid neoplasms; **AND**
        - Used as a single agent; **OR**
    - Patient has blast phase lymphoid, myeloid, or mixed lineage neoplasms; **AND**
        - Used in combination with ALL- or AML-type induction chemotherapy followed by allogeneic HCT (if eligible)

† FDA Approved Indication(s); ‡ Compendia Recommended Indication(s); Φ Orphan Drug

IV. Renewal Criteria [1-4,7]

Coverage can be renewed based upon the following criteria:

- Patient continues to meet universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: arterial occlusive events, venous thromboembolic events, hepatotoxicity, ocular toxicity, serious or severe hypertension, hypertensive crisis, heart failure, pancreatitis, serious hemorrhage, fluid retention (peripheral edema, pleural effusion, and pericardial effusion), cardiac arrhythmias, Grade 3 or 4 myelosuppression, tumor lysis syndrome (TLS), gastrointestinal perforation, impaired wound healing, neuropathy, reversible posterior leukoencephalopathy syndrome (RLPS), etc.; **AND**

Acute Lymphoblastic Leukemia (ALL)

- Treatment response or stabilization of disease as indicated by CBC, bone marrow cytogenic analysis, QPCR, or FISH

Chronic Myelogenous Leukemia (CML)

- Re-escalating treatment due to loss of response on a reduced dose (CP-CML or AP-CML only); **OR**
- Treatment response as indicated by one of the following *BCR-ABL1* (IS) transcript levels:
  - > 0.1% to 10% at 3 months or 6 months; **OR**
  - > 0.1% to 1% at 12 months and beyond (if treatment goal is long-term survival); **OR**
  - ≤ 0.1% at 12 months and beyond (if treatment goal is treatment-free remission)

  NOTE: cytogenetic assessment of response may be used if quantitative RT-PCR (QPCR) using International Scale (IS) for *BCR-ABL1* is not available

Myeloid/Lymphoid Neoplasms with Eosinophilia

- Disease response as evidenced by at least one of the following:
  - Decrease in spleen size or improvements in other myelofibrosis symptoms (such as fatigue, bone pain, frequent infections, fever, night sweats, easy bruising/bleeding, etc.)
  - Stabilization or improvement as evidenced by a complete response [CR] (i.e. morphologic, cytogenetic or molecular complete response CR), complete hematologic response, or a partial response by CBC, bone marrow cytogenic analysis, QPCR, or FISH

V. Dosage/Administration [1,7]

Indication	Dose
CP-CML	Starting dosage is 45 mg administered orally once daily with a reduction to 15 mg once daily upon achievement of ≤1% BCR-ABL1. Continue treatment until loss of response at the re-escalated dose or unacceptable toxicity. • Patients with loss of response can re-escalate to a previously tolerated dosage of 30 mg or 45 mg orally once daily. • Consider discontinuing if hematologic response has not occurred by 3 months.
AP-CML, BP-CML, and Ph+ ALL	45 mg administered orally once daily • Consider reducing the dose for patients with accelerated phase (AP) CML who have achieved a major cytogenetic response. • Continue until loss of response or unacceptable toxicity. • Consider discontinuing if response has not occurred by 3 months.
Myeloid/Lymphoid Neoplasms with Eosinophilia	45 mg administered orally once daily

VI. Billing Code/Availability Information

HCPCS Code:

- J8999: Prescription drug, oral, chemotherapeutic, NOS

NDC(s):

- Iclusig 10 mg tablet: 63020-0536-xx
- Iclusig 15 mg tablet: 63020-0535-xx
- Iclusig 30 mg tablet: 63020-0533-xx
- Iclusig 45 mg tablet: 63020-0534-xx

VII. References

1. Iclusig [package insert]. Cambridge, MA; Takeda Pharmaceuticals Company Limited; February 2022. Accessed June 2022.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for Acute Lymphoblastic Leukemia. 1.2022. National Comprehensive Cancer Network, 2022. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed June 2022.
3. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for Chronic Myelogenous Leukemia 3.2022. National Comprehensive Cancer Network, 2022. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed June 2022.
4. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for ponatinib. National Comprehensive Cancer Network, 2022. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed June 2022.
5. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. N Engl J Med. 2013;369(19):1783-1796. doi:10.1056/NEJMoa1306494.
6. Gutierrez VG, Cortes J, Deininger M, et al. The OPTIC Study: a Multi-Center, Randomized Phase 2 Trial with Response-Based Dose Reduction to Evaluate Three Starting Doses of Ponatinib. Volume 16, Supplement 2, S59-S60, September 01, 2016. DOI:https://doi.org/10.1016/j.clml.2016.07.086.
7. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes. Version 1.2022. National Comprehensive Cancer Network, 2022. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed June 2022.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C83.50	Lymphoblastic (diffuse) lymphoma, unspecified site
C83.51	Lymphoblastic (diffuse) lymphoma, lymph nodes of head, face, and neck
C83.52	Lymphoblastic (diffuse) lymphoma, intrathoracic lymph nodes
C83.53	Lymphoblastic (diffuse) lymphoma, intra-abdominal lymph nodes
C83.54	Lymphoblastic (diffuse) lymphoma, lymph nodes of axilla and upper limb
C83.55	Lymphoblastic (diffuse) lymphoma, lymph nodes of inguinal region and lower limb
C83.56	Lymphoblastic (diffuse) lymphoma, intrapelvic lymph nodes
C83.57	Lymphoblastic (diffuse) lymphoma, spleen
C83.58	Lymphoblastic (diffuse) lymphoma, lymph nodes of multiple sites
C83.59	Lymphoblastic (diffuse) lymphoma, extranodal and solid organ sites
C91.00	Acute lymphoblastic leukemia, not having achieved remission
C91.01	Acute lymphoblastic leukemia, in remission
C91.02	Acute lymphoblastic leukemia, in relapse
C92.10	Chronic myeloid leukemia, BCR/ABL-positive, not having achieved remission
C92.11	Chronic myeloid leukemia, BCR/ABL-positive, in remission
C92.12	Chronic myeloid leukemia, BCR/ABL-positive, in relapse
C94.8	Other specified leukemias
C94.80	Other specified leukemias not having achieved remission
C94.81	Other specified leukemias not having achieved remission
C94.82	Other specified leukemias, in relapse
C95.1	Other specified leukemias, in relapse
C95.10	Chronic leukemia of unspecified cell type not having achieved remission
C95.11	Chronic leukemia of unspecified cell type, in remission
C95.12	Chronic leukemia of unspecified cell type, in relapse
C96.Z	Other specified malignant neoplasms of lymphoid, hematopoietic and related tissue
C96.9	Malignant neoplasm of lymphoid, hematopoietic and related tissue, unspecified

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at: https://www.cms.gov/medicare-coverage-database/search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC