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 [1,4]

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**
- Patient has Ph+ B-ALL ‡; **AND**
  - Used for relapsed or refractory disease; **AND**
    - Used as a single agent; **OR**
    - Used in combination inotuzumab ozogamicin; **OR**
    - Used in combination with blinatumomab; **OR**
  - Used as maintenance therapy; **AND**
    - Used in combination with POMP regimen (vincristine and prednisone with or without methotrexate and mercaptopurine); **AND**
      - Used following consolidation therapy for patients with negative minimal residual disease (if not already included in a multi-part regimen); **OR**
    - Used as single agent therapy; **AND**
      - Used post-hematopoietic stem cell transplant; **OR**
      - Used in patients unfit for additional therapies; **OR**
  - Used as induction therapy; **AND**
    - Used as frontline therapy OR for relapsed/refractory disease (if not previously given); **AND**
      - Used in combination with a corticosteroid; **OR**
      - Used in combination with vincristine and dexamethasone; **OR**
      - Used as a component of a multiagent chemotherapy regimen *(Note: May be used in patients at least 15 years of age)*; **OR**
  - Used as consolidation therapy; **AND**
    - Used for relapsed/refractory disease (if not previously given); **AND**
      - Used as a component of a multiagent chemotherapy regimen *(Note: May be used in patients at least 15 years of age)*; **OR**
    - Used as frontline therapy; **AND**
      - Used as a component of a multiagent chemotherapy regimen *(Note: May be used in patients at least 15 years of age)*; **OR**
      - Used as single agent therapy in patients unfit for additional therapies; **OR**
      - Used in combination with blinatumomab; **AND**

- Used for persistent/rising minimal residual disease after complete response to induction therapy; **OR**
- Used for negative minimal residual disease after complete response to induction therapy if patient is not a candidate for multiagent therapy

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 primary treatment with one of the following: imatinib, bosutinib, dasatinib, or nilotinib; **AND**
    - Patient has chronic phase disease; **AND**
    - Patient has T315I mutation positive disease; **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)

Gastrointestinal Stromal Tumors (GIST) ‡ [4,8]

- Used as a single agent; **AND**
- Patient has gross residual (R2 resection), unresectable primary, recurrent, or metastatic disease OR tumor rupture; **AND**
- Disease has progressed on imatinib, sunitinib, regorafenib, and ripretinib

† 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:
  - ≤ 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 and Tyrosine Kinase Fusion Genes ‡

- Disease response as evidenced by at least one of the following:
  - Decrease in spleen size or improvements in other myelofibrosis symptoms (such as weakness, fatigue, cough, dyspnea, myalgias, angioedema, rash, fever, rhinitis, 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

Gastrointestinal Stromal Tumors (GIST) ‡

- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread

V. Dosage/Administration [1,7,8]

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
GIST	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 2023.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for Acute Lymphoblastic Leukemia. 1.2023. National Comprehensive Cancer Network, 2023. 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 2023.
3. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for Chronic Myelogenous Leukemia 2.2023. National Comprehensive Cancer Network, 2023. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES®

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4. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for ponatinib. National Comprehensive Cancer Network, 2023. 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 2023.
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 1.2023. National Comprehensive Cancer Network, 2023. 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 2023.
8. George S, Mehren M, Fletcher J, et al. Phase II Study of Ponatinib in Advanced Gastrointestinal Stromal Tumors: Efficacy, Safety, and Impact of Liquid Biopsy and Other Biomarkers. Clinical Trial: Clin Cancer Res. 2022 Apr 1;28(7):1268-1276. doi: 10.1158/1078-0432.CCR-21-2037.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C49.A0	Gastrointestinal stromal tumor unspecified site
C49.A1	Gastrointestinal stromal tumor of esophagus
C49.A2	Gastrointestinal stromal tumor of stomach
C49.A3	Gastrointestinal stromal tumor of small intestine
C49.A4	Gastrointestinal stromal tumor of large intestine
C49.A5	Gastrointestinal stromal tumor of rectum
C49.A9	Gastrointestinal stromal tumor of other sites
C49.4	Malignant neoplasm of connective and soft tissue of abdomen
C49.5	Malignant neoplasm of connective and soft tissue of pelvis
C49.8	Malignant neoplasm of overlapping sites of connective and soft tissue
C49.9	Malignant neoplasm of connective and soft tissue, unspecified

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
Z85.831	Personal history of malignant neoplasm of soft tissue

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
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
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